Single Technology Appraisal

Pembrolizumab with carboplatin and paclitaxel for untreated advanced or recurrent endometrial cancer [ID6381]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pembrolizumab with carboplatin and paclitaxel for untreated advanced or recurrent endometrial cancer [ID6381]

Contents:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pembrolizumab with platinum-based chemotherapy then pembrolizumab maintenance for treating advanced or recurrent endometrial cancer [ID6381]

MMR Subgroups

February 2025

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Background

This document supplements the analyses presented in the Company submission (CS; Document B and Appendices). It presents the deterministic base case, deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA) results separately for the dMMR and pMMR subgroups, reflecting the inputs and assumptions described in the Company submission, as well as key scenario analyses for the subgroups, aligned with those previously defined and presented for the all-comers cohort.

Further details on the selection of base case PFS and OS extrapolations are also provided for transparency to aid review. The approach to survival extrapolation and curve selection used for the all-comer population (as described in Section B.3.3 of the Company submission) was also applied to the MMR subgroups. The curve extrapolations for the dMMR and pMMR subgroups were presented to clinical experts during the advisory board held in July 2024.

An overview of the other data inputs used in the analyses by MMR status was provided in Table 57 of the Company submission Appendix.

Two accompanying Excel models are provided alongside this document, saved with the base case settings and sensitivity and scenario analysis results for each MMR subgroup. These models are consistent with the previously submitted Company model, with three minor edits:

- correction of the terminal care cost to £8,829.07 as discussed in clarification questions and implemented in the EAG's model
- correction of the health state utility input values for the scenario analysis using Swedish utility values from KEYNOTE-775 (previously, the PF and PD utilities were assigned to the incorrect health state)
- addition of a summary table on the 'PSA Results' sheet to display the results of the PSA for quick reference

1 dMMR

1.1 Curve extrapolation and selection process

1.1.1 PFS

Table 1. Overview of PFS curve selection: dMMR

	Summary of selection
CT arm	
Statistical fit and visual fit to the KM data	• All standard parametric extrapolations produced a very poor visual fit to the observed KM data (CS Appendix Figure 45) and were therefore excluded from consideration. • Two-piece curves with a 27-week cut point provided an improved visual fit to the KM data and hazard profile, except for exponential and Gompertz. Generalised gamma fit well but likely overfit to the tail (CS Appendix Figure 47−48). • Splines provided a good fit to the KM data and generally fit the hazard profile well but were likely to be overfit to the tails (CS Appendix Figure 49−52). AIC/BIC values were improved compared with standard parametric models (CS Appendix Table 60 and Table 62).
Clinical plausibility	• Clinical experts estimated that 5-10% and 3-5% of dMMR patients treated with CT in the first-line setting would be alive and progression-free at 5 years and 10 years, respectively (Table 2). This confirmed that all of the spline models and several of the two-piece models were too optimistic in terms of PFS estimates for this group. • Two-piece curves were considered by the experts who agreed that the two-piece gamma curve was the most realistic and representative of expectations (note Gompertz and exponential curves were not presented due to implausibly high tail and poor visual fit, respectively). As this curve also had good visual fit this was selected for the base case. • Company advisors as part of NICE TA963 were slightly more optimistic in their estimates of long-term PFS in this group, suggesting that PFS rates would be 9% at 5 years and 7% at 10 years; a scenario analysis using two-piece Weibull was therefore conducted to explore this.
Selected	Base case: • **Two-piece gamma** Scenarios: • Two-piece Weibull
Pembrolizumab + CT	
Statistical fit and visual fit to the KM data	• Several of the standard parametric models provided a good fit to the observed KM data and hazards profile, whilst others (exponential, Weibull and gamma) predicted a virtually constant hazard that did not reflect the observed trend (CS Appendix Figure 61 and Figure 62). AIC/BIC values varied within a small range of 2-6 points (CS Appendix Table 66). Generalised gamma or log-normal provided the best overall balance of visual and statistical fit. • Two-piece models with a 27-week cut point were explored, and whilst they provided good visual fit to the KM data and hazard profile (CS

	Appendix Figure 63 and Figure 64), they were generally less preferred for the base case due to the already small sample size in this group. • Splines also generally provided good visual fit to the KM data, except for the 3-knot odds which underestimated the short-term KM and then appeared to overfit the tail (CS Appendix Figure 65). However, all 2- and 3-knot splines appeared to represent the hazard profile poorly; 1-knot splines offered a reasonable fit, but with no meaningful improvement vs the standard models (CS Appendix Figure 66−68). AIC/BIC values were comparable or slightly higher than those for standard models (CS Appendix Table 66 and Table 68).
Clinical plausibility	• Standard parametric models were presented to clinical experts who agreed that, of these, the generalised gamma, log-logistic and log-normal curves were the most clinically plausible and representative of expectations. • However, several advisors also stated that the tail of the curve should be flatter, and the plateau should begin sooner than any of these curves predicted, as dMMR EC responds very well to immunotherapy. This is consistent with the mean landmark estimates provided by company and EAG advisors in NICE TA963 (Table 3). • Considering the statistical and visual fit, available sample size, and long-term extrapolations, the standard generalised gamma was selected for the base case. • However, given the advisors' comments regarding the long-term shape of the PFS curve, response to immunotherapy in the dMMR group, and landmark estimates in NICE TA963, a scenario predicting more optimistic long-term estimates was explored. The two-piece log-logistic provided 10- and 20-year estimates that aligned well with the estimates from advisors in TA963 and was therefore selected for the scenario analysis.
Selected	Base case: • **Standard generalised gamma** Scenarios: • Two-piece log-logistic

Table 2. Landmark PFS estimates, CT: dMMR

Estimates	**Years**			
	2	**5**	**10**	**20**
MSD Clinical Experts – dMMR	15%	5-10%	3-5%	NR
NICE TA963 company advisors' estimates for 1L dMMR EC patients receiving CT	23%	9%	7%	6%
Two-piece parametric models (KEYNOTE-868 [NRG-GY018])				
2P Exponential	[redacted]	[redacted]	[redacted]	[redacted]
2P Weibull	[redacted]	[redacted]	[redacted]	[redacted]
2P Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
2P Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
2P Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
2P Gamma	[redacted]	[redacted]	[redacted]	[redacted]
2P Generalized Gamma	[redacted]	[redacted]	[redacted]	[redacted]

Landmark estimates have not been adjusted for background mortality.
Model in bold selected for the base case.
*Models in *grey italics* excluded due to clinical implausibility based on clinical experts' estimates.

Table 3. Landmark PFS estimates, pembrolizumab + CT: dMMR

Estimates	Years			
	2	5	10	20
NICE TA963 company and EAG advisors' mean for 1L dMMR EC patients receiving dostarlimab (anti-PD-1) + CT	60%	42%	33%	27%
Standard parametric models (KEYNOTE-868 [NRG-GY018])				
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Generalized Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Two-piece parametric models (KEYNOTE-868 [NRG-GY018])				
2P Exponential	[redacted]	[redacted]	[redacted]	[redacted]
2P Weibull	[redacted]	[redacted]	[redacted]	[redacted]
2P Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
2P Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
2P Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
2P Gamma	[redacted]	[redacted]	[redacted]	[redacted]
2P Generalized Gamma	[redacted]	[redacted]	[redacted]	[redacted]

Landmark estimates have not been adjusted for background mortality
Model in bold selected for the base case.
*Models in *grey italics* excluded due to clinical implausibility based on clinical experts' estimates.

Figure 1. Selected base case and scenario curves for PFS: dMMR

[redacted]

1.1.2 OS

Table 4. Overview of OS curve selection: dMMR

	Summary of selection
CT arm	
Statistical fit and visual fit to the KM data	• All standard parametric models provided a similar and reasonable fit to the observed KM and hazard profile (CS Appendix Figure 53 and Figure 54). Exponential had the lowest AIC/BIC and all except generalised gamma had AIC/BIC values within 5 points of this. • As there was no obvious turning point in the hazard profile and given the already small sample size of the dMMR population, two-piece models were not considered (although models were fit to the data for completeness [CS Appendix Figure 55−56, Table 64]). • Spline models were also explored. They offered a reasonable fit to the KM data (CS Appendix Figure 57) but provided no improvement vs standard parametric models and overall had higher AIC/BIC values (CS

	Appendix Table 63 and Table 65). All 2- and 3-knot splines had a relatively poor fit to the hazard profile, and while 1-knot splines had a reasonable fit, again there was no improvement vs standard models (CS Appendix Figure 58−60). They were therefore not considered further.
Clinical plausibility	• Clinical experts estimated that 40-50% and 20% of dMMR patients who received CT in the first-line would be alive at 5 years and 10 years, respectively. • The experts reviewed the standard parametric models and considered the exponential, log-logistic and generalised gamma to be plausible options. • Of these, exponential had the best alignment with the MSD experts' landmark estimates at 5- and 10 years and had the lowest AIC/BIC. It was therefore selected for the base case analysis. • A scenario analysis using the gamma parametric model curve, to align with long-term predictions from advisors in NICE TA963, was also conducted.
Selected	Base case: • **Standard exponential** Scenarios: • Standard gamma
Pembrolizumab + CT	
Statistical fit and visual fit to the KM data	• All standard extrapolations provided an acceptable fit to the KM data and hazard profile, although the gamma, Weibull and exponential distributions provided very flat hazard profiles which did not fully reflect the observed hazard trend (CS Appendix Figure 69−70). AIC/BIC values were comparable and remained within 5 points of the exponential, which had the best statistical fit; only BIC for generalised gamma was outside this range (CS Appendix Table 69). • As with the CT arm, there was no obvious turning point in the hazard profile and, given the already small sample size of the dMMR population, two-piece models were not considered (although models were fit to the data for completeness [CS Appendix Figure 71−72, Table 70]). • Spline models were explored, however several of these did not converge (2-knot hazard, all 3-knot splines) and those that did converge had poorer AIC/BIC compared with standard models (CS Appendix Table 69 and Table 71). Similarly, hazard fits were not improved vs the standard parametric models (CS Appendix Figure 74−75), therefore splines were also not considered further.
Clinical plausibility	• Clinical experts initially stated a preference for the Weibull or gamma distributions. However, both these curves fell significantly below the landmark estimates provided by advisors in NICE TA963, and the expectations of the clinical experts at the NICE TA963 committee meeting were that the OS for anti-PD-1 treatment would be closer to the company's advisors' estimates than the EAG's. • In addition, Weibull and gamma curves did not provide a good fit to the observed hazard profiles, as they predicted almost constant or increasing hazard rates over time which does not reflect the observed trend for decreasing hazards or the non-monotonic trend observed for the pembrolizumab + CT arm in the (larger) pMMR and all comers cohorts.

	• Taking all this into account, the log-logistic was considered to provide the best balance of fit and long-term OS estimates based on clinical insights from the advisory board and NICE TA963 and was therefore selected for the base case. This provided OS estimates that sit well below the company advisors' estimates from NICE TA963 but that aligned reasonably well with the mean company and EAG advisor's estimates from TA963. • Scenario analyses were also conducted to explore the impact of a more conservative (exponential) and more optimistic (log-normal) OS extrapolations.
Selected	Base case: • **Standard log-logistic** Scenarios: • Exponential • Log-normal

Table 5. Landmark OS estimates, CT: dMMR

Estimates	Years			
	2	5	10	20
MSD Clinical Experts – dMMR	65-75%	40-50%	20%	NR
NICE TA963 company and EAG advisors' mean estimates for 1L dMMR EC patients receiving CT	58%	27%	15%	11%
Standard parametric models (KEYNOTE-868 [NRG-GY018])				
Exponential	**72%**	**44%**	**19%**	**4%**
Weibull	72%	40%	14%	1%
Log-normal	*72%*	*50%*	*33%*	*18%*
Log-logistic	71%	45%	26%	13%
Gompertz	72%	42%	14%	1%
Gamma	72%	40%	14%	2%
Generalized Gamma	72%	47%	28%	12%

Landmark estimates adjusted for background mortality.
Model in bold selected for the base case.
*Models in *grey italics* excluded due to clinical implausibility based on clinical experts' estimates.

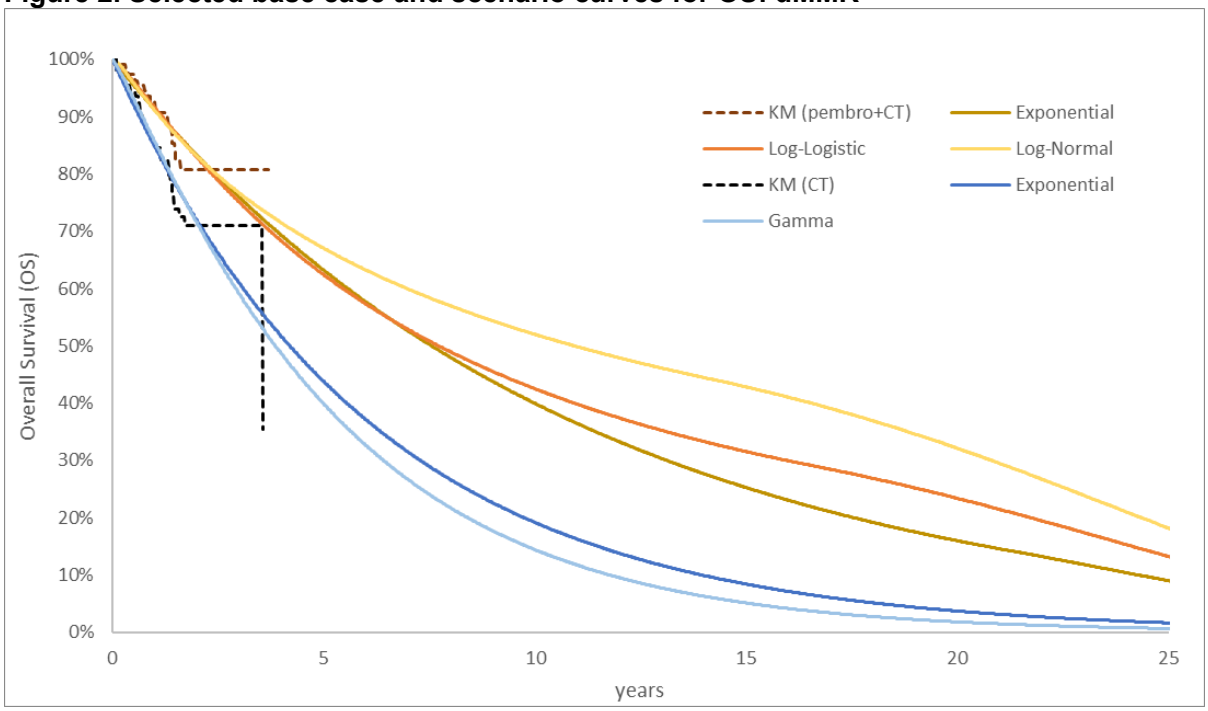
Table 6. Landmark OS estimates, pembrolizumab + CT: dMMR

Estimates	Years			
	2	5	10	20
NICE TA963 company advisors' estimates for 1L dMMR EC patients receiving dostarlimab (anti-PD-1) + CT	82%	67%	53%	44%
NICE TA963 company and EAG advisors' mean estimates for 1L dMMR EC patients receiving dostarlimab (anti-PD-1) + CT	82%	59%	46%	38%
Standard parametric models (KEYNOTE-868 [NRG-GY018])				
Exponential	83%	63%	40%	16%
Weibull	83%	61%	35%	10%

Log-normal	83%	67%	52%	32%
Log-logistic	**83%**	**62%**	**43%**	**23%**
Gompertz	83%	68%	56%	36%
Gamma	83%	61%	35%	11%
Generalized Gamma	83%	65%	48%	28%

Landmark estimates adjusted for background mortality.
Model in bold selected for the base case.

Figure 2. Selected base case and scenario curves for OS: dMMR



1.2 Results

1.2.1 Deterministic base case results

Table 7. Deterministic base case results: dMMR

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Pembrolizumab + CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2.12	[redacted]
CT	[redacted]	5.01	[redacted]	-	-	-	-

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

1.2.2 Probabilistic results

Table 8. Mean probabilistic base case results: dMMR

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Pembrolizumab + CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.85	[redacted]
CT	[redacted]	4.99	[redacted]	-	-	-	-

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Figure 3. Cost effectiveness plane, pembrolizumab + CT versus CT: dMMR

[redacted]

Figure 4. Cost effectiveness acceptability curve, pembrolizumab + CT versus CT: dMMR

[redacted]

1.2.3 Deterministic sensitivity analysis

Figure 5. Tornado diagram, top 10 parameters: dMMR

[redacted]

1.2.4 Scenario analyses

Table 9. Scenario analyses: dMMR

#	Category	Base case value	Scenario value	Rationale	Inc. Costs	Inc. QALYs	ICER	% change
-	**Base case**				[redacted]	**2.12**	[redacted]	
1	Time horizon	35	10	Estimating impact if a shorter time-horizon is selected	[redacted]	0.99	[redacted]	97%
2		35	20		[redacted]	1.86	[redacted]	10%
3	Discount rate (costs and utilities)	3.5%	1.5%	As per NICE guidance	[redacted]	2.68	[redacted]	-17%
4	Impact of AE (cost and disutilities)	Include	Exclude	Remove potential double counting of impact of AEs	[redacted]	2.12	[redacted]	0%
5	Utility values	KN-158	KN-826 TTD	Explore a wide range of utility sources given that trial-based EQ-5D was not available from KEYNOTE-868 (NRG-GY018)	[redacted]	2.19	[redacted]	-3%
6		KN-158	KN-826 progression-based		[redacted]	2.16	[redacted]	-2%
7		KN-158	KN-775 (Swedish value set)		[redacted]	2.51	[redacted]	-15%
8		KN-158	KN-775 (Australian value set)		[redacted]	2.15	[redacted]	-1%
9	Subsequent treatment	Re-weighted trial-based treatment mix based on UK clinician inputs	Per KEYNOTE-868 (NRG-GY018)	Understand the impact of using different subsequent treatment composition in the UK, including IO	[redacted]	2.12	[redacted]	17%
10	Subsequent treatment (CT): dostarlimab	Dostarlimab: 0.00%	Dostarlimab takes pembrolizumab monotherapy share	Estimate impact of a scenario where dostarlimab becomes standard of care for 2L	[redacted]	2.12	[redacted]	-41%

#	Category	Base case value	Scenario value	Rationale	Inc. Costs	Inc. QALYs	ICER	% change
11	Healthcare resource utilisation	UK clinician inputs	Healthcare resource use reported in TA963	Estimate impact of a different healthcare resource utilisation pattern	[redacted]	2.12	[redacted]	8%
12	OS extrapolation	Pembrolizumab + CT: Log-logistic CT: Exponential	Pembro + CT: Log-logistic CT: **Gamma**	To reflect more optimistic long-term OS estimates in NICE TA963	[redacted]	2.43	[redacted]	-11%
13			Pembro + CT: **Log-normal** CT: Exponential	To reflect more optimistic long-term OS estimates in NICE TA963	[redacted]	2.79	[redacted]	-21%
14			Pembro + CT: **Exponential** CT: Exponential	To explore more conservative long-term OS estimates	[redacted]	1.85	[redacted]	13%
15	PFS extrapolation	Pembro + CT: Gen gamma CT: 2P gamma	Pembro + CT: Gen gamma CT: **2P Weibull**	To reflect more optimistic long-term PFS estimates in NICE TA963	[redacted]	2.11	[redacted]	2%
16			Pembro + CT: **2P log-logistic** CT: 2P gamma	To reflect more optimistic long-term PFS estimates in NICE TA963	[redacted]	2.15	[redacted]	-2%
17	PFS and OS extrapolations	<u>PFS</u> Pembrolizumab + CT: Log-logistic CT: Exponential <u>OS</u> Pembro + CT: Gen gamma CT: 2P gamma	<u>PFS</u> Pembro + CT: **2P log-logistic** CT: **2P Weibull** <u>OS</u> Pembro + CT: **Log-normal** CT: **Gamma**	To better reflect PFS and OS estimates favoured by company clinical experts in NICE TA963	[redacted]	3.12	[redacted]	-28%
18	Treatment waning	No waning	Applied to 17.9% of pembrolizumab + CT dMMR patients. Assumed	In accordance with previous IO therapies in endometrial cancer, waning is applied to patients who did not have an	[redacted]	2.00	[redacted]	6%

#	Category	Base case value	Scenario value	Rationale	Inc. Costs	Inc. QALYs	ICER	% change
			start at 7 years (post treatment initiation) for 2 years before effect of CT is assumed	ORR. It is applied from 7 years based on the long-term follow-up reported in KEYNOTE-006 where no evidence of treatment effect waning is observed.				

Key: 2L, second-line; AE, adverse event; CT, paclitaxel + carboplatin; IO, immunotherapy; ICER, incremental cost effectiveness ratio; ITT, intention to treat; KM, Kaplan–Meier; NICE, National Institute of Health and Care Excellence; OS, overall survival; PFS, progression-free survival; TOT, time on treatment; TTD, time to treatment discontinuation.

2 pMMR

2.1 Curve extrapolation and selection process

2.1.1 PFS

Table 10. Overview of PFS curve selection: pMMR

	Summary of selection
CT arm	
Statistical fit and visual fit to the KM data	• All standard extrapolations had a poor visual fit to observed KM data (CS Appendix Figure 76) and hazard profile (CS Appendix Figure 77) and were therefore excluded from consideration. • Two-piece (2P) curves with a 37-week cut point provided a good visual fit to the KM data (CS Appendix Figure 78) and hazard profile (CS Appendix Figure 79), with the exception of the 2P exponential which was therefore excluded. • Spline models also provided an excellent visual fit to the KM data and hazards (CS Appendix Figures 80−83). The statistical fit in terms of AIC/BIC was improved for all splines compared with the standard parametric extrapolations (CS Appendix Table 72 and Table 74), and varied within a small range.
Clinical plausibility	• Clinical experts suggested that PFS rates for this group would be 2-3% at 5 years and 1-2% at 10 years (Table 11). This ruled out the 2P log-logistic, log-normal and Gompertz curves, and all 2- and 3-knot splines due to implausibly high tails. • The remaining 2P curves were presented to clinical experts at the advisory board (no splines were presented at the advisory board due to their unavailability at the time). • The experts supported the 2P exponential curve as clinically plausible but agreed that a 0% PFS rate at 10 years is unlikely. • 1-knot odds spline was highly concordant with the 2P exponential but predicted that a small proportion would remain progression-free at 10 years, thus offering better alignment with expert predictions. It was therefore selected for the base case.
Selected	Base case: • **Spline 1-knot odds**
Pembrolizumab + CT	
Statistical fit and visual fit to the KM data	• All standard extrapolations had a poor visual fit to observed KM data (CS Appendix Figure 92) and hazard profile (CS Appendix Figure 93) and were therefore excluded from consideration. • Two-piece (2P) curves with a 37-week cut point provided a good visual fit to the KM data (CS Appendix Figure 94) and hazard profile (CS Appendix Figure 95), with the exception of the 2P exponential which was therefore excluded. AIC/BIC values for Weibull, log-normal, gamma and generalised gamma ranged within 5 points of each other; the remaining curves had much higher AIC/BIC values and were therefore unlikely to represent the data well. • Amongst spline models, all 2- and 3-knot splines had an excellent fit to the KM data and hazard profile and had lower AIC/BIC statistics

	compared with the standard models. All 1-knot splines had AIC/BIC values more than 10-15 points higher than the 2- and 3-knot splines and failed to capture the shape of the second half of the observed KM data, therefore they likely underestimate long-term PFS (CS Appendix Figure 96−99, Table 78, Table 80).
Clinical plausibility	• Two-piece curves were considered further by clinical experts (note 2P exponential, Gompertz and log-logistic were not presented due to poor visual/statistical fit). Splines were not presented at the advisory board due to their unavailability at the time. • Clinical experts supported the 2P generalised gamma or Weibull curves as most clinically plausible and representative of expectations. Both have similar AIC, but the generalised gamma provided a better fit to the observed hazards in the tail and was therefore preferred. • Long-term estimates for the 3-knot spline models were deemed too optimistic based on clinical experts' preferred 2P curves and were therefore excluded. Of the remaining (2-knot) splines, the 2-knot normal provided the most modest long-term estimates and sits between the 2P log-normal and 2P generalised gamma curves presented to experts and was therefore considered for a scenario analysis (Table 12).
Selected	Base case: • **Two-piece (2P) generalised gamma** Scenarios: • Two-piece (2P) Weibull • Spline 2-knot normal

Table 11. Landmark PFS estimates, CT: pMMR

Estimates	**Years**			
	2	**5**	**10**	**20**
MSD Clinical Experts – pMMR	10%	2-3%	1-2%	NR
Two-piece parametric models (KEYNOTE-868 [NRG-GY018])				
2P Exponential	[redacted]	[redacted]	[redacted]	[redacted]
2P Weibull	[redacted]	[redacted]	[redacted]	[redacted]
2P Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
2P Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
2P Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
2P Gamma	[redacted]	[redacted]	[redacted]	[redacted]
2P Generalized Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Spline models (KEYNOTE-868 [NRG-GY018])				
Hazard, k=1	[redacted]	[redacted]	[redacted]	[redacted]
Normal, k=1	[redacted]	[redacted]	[redacted]	[redacted]
Odds, k=1	[redacted]	[redacted]	[redacted]	[redacted]
Hazard, k=2	[redacted]	[redacted]	[redacted]	[redacted]
Normal, k=2	[redacted]	[redacted]	[redacted]	[redacted]
Odds, k=2	[redacted]	[redacted]	[redacted]	[redacted]
Hazard, k=3	[redacted]	[redacted]	[redacted]	[redacted]
Normal, k=3	[redacted]	[redacted]	[redacted]	[redacted]

Odds, k=3	[redacted]	[redacted]	[redacted]	[redacted]

Landmark estimates have not been adjusted for background mortality.
Model in bold selected for the base case.
*Models in *grey italics* excluded due to clinical implausibility based on clinical experts' estimates.

Table 12. Landmark PFS estimates, pembrolizumab + CT: pMMR

Estimates	Years			
	2	5	10	20
MSD Clinical Experts – pMMR CT (lower bound)	10%	2-3%	1-2%	NR
Two-piece parametric models (KEYNOTE-868 [NRG-GY018])				
2P Exponential	[redacted]	[redacted]	[redacted]	[redacted]
2P Weibull	[redacted]	[redacted]	[redacted]	[redacted]
2P Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
2P Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
2P Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
2P Gamma	[redacted]	[redacted]	[redacted]	[redacted]
2P Generalized Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Spline models (KEYNOTE-868 [NRG-GY018])				
Hazard, k=1	[redacted]	[redacted]	[redacted]	[redacted]
Normal, k=1	[redacted]	[redacted]	[redacted]	[redacted]
Odds, k=1	[redacted]	[redacted]	[redacted]	[redacted]
Hazard, k=2	[redacted]	[redacted]	[redacted]	[redacted]
Normal, k=2	[redacted]	[redacted]	[redacted]	[redacted]
Odds, k=2	[redacted]	[redacted]	[redacted]	[redacted]
Hazard, k=3	[redacted]	[redacted]	[redacted]	[redacted]
Normal, k=3	[redacted]	[redacted]	[redacted]	[redacted]
Odds, k=3	[redacted]	[redacted]	[redacted]	[redacted]

Landmark estimates have not been adjusted for background mortality
Model in bold selected for the base case.
*Models in *grey italics* excluded due to clinical implausibility based on clinical experts' estimates.

Figure 6. Selected base case and scenario curves for PFS: pMMR

[redacted]

2.1.2 OS

Table 13. Overview of OS curve selection: pMMR

	Summary of selection
CT arm	
Statistical fit and visual fit to the KM data	• All standard extrapolations provided a good fit to the KM data (CS Appendix Figure 84) and represented the steadily increasing hazard profile well (CS Appendix Figure 85), except the exponential which was therefore excluded from consideration. The log-normal appeared to slightly overestimate observed OS at the tail whilst Gompertz likely underestimated the tail.

	• Gamma had the lowest AIC/BIC values, and all curves except for Gompertz and exponential ranged within 5 points of this best-fitting curve (CS Appendix Table 75). • Two-piece (2P) curves with a 60-week cut point were also explored. All curves fit the observed KM data well (CS Appendix Figure 86), except log-normal and log-logistic which overestimated the tail. The 2P exponential appeared to best represent the observed hazards (CS Appendix Figure 87), however there was no clear improvement in fit with any 2P model versus the standard parametric curves and the late cut point resulted in loss of data meaning extrapolations may be more unstable – therefore 2P were not preferred over standard models. The 2P exponential had the lowest AIC/BIC, although all curves remained within 5 points (CS Appendix Table 76). • All spline models provided an excellent fit to the KM data (CS Appendix Figure 88). The 1-knot hazard had the lowest AIC/BIC but all 1- and 2-knot splines remained within 6 points of this, and overall statistical fit was comparable to the standard models (CS Appendix Table 75 and Table 77). 1-knot splines offered no improvement in hazard profile fit versus standard models, but 2-knot splines did appear to provide a closer representation of the observed hazard profile (CS Appendix Figure 89−91).
Clinical plausibility	• Clinical experts considered the standard parametric models (excluding exponential, due to poor visual/statistical fit, and splines which were not available at the time) and felt that the gamma curve was the most appropriate. As gamma also had the best statistical fit of all standard and spline models, and had a good fit to the hazard profile, this was selected as the base case. • Experts also considered that the OS tail could potentially be raised slightly, therefore alternative curves with a slightly raised tail were explored in scenario analyses. Generalised gamma provided a more optimistic tail and was therefore a suitable alternative standard model. Amongst the splines, the 2-knot splines provided good statistical fit and improved hazard profile fit vs 1-knot models, with 2-knot odds providing the most optimistic option with the flattest tail.
Selected	Base case: • **Standard gamma** Scenarios: • Generalised gamma • Spline 2-knot odds
Pembrolizumab + CT	
Statistical fit and visual fit to the KM data	• All standard parametric extrapolations had good alignment with the observed KM data, except exponential. Log-normal fit well in the short term but likely overestimated the tail (CS Appendix Figure 100). Gompertz, log-normal and exponential were a poot fit to the hazard profile; the remaining models had a reasonable alignment in the short term, but only the log-logistic captured the overall shape, including the turning point (CS Appendix Figure 101). All standard models (except exponential and log-normal) were within 5 points of the model with the lowest AIC/BIC (Weibull). • Two-piece (2P) models with a 60-week cut point had good visual fit to the KM data (CS Appendix Figure 102), had AIC/BIC values within 5 points of each other (CS Appendix Table 82), and all curves except exponential, Weibull and gamma offered a reasonable representation of

	the hazard profile (CS Appendix Figure 103). However, the late cut point resulted in loss of data meaning extrapolations may be more unstable. • All spline models fit the observed KM data well (CS Appendix Figure 104), however there was no improvement in statistical fit (AIC/BIC) compared with the standard parametric models (CS Appendix Table 81 and Table 83). All hazard splines poorly represented the hazard profile, whilst the complexity of 3-knot splines resulted in unusual hazard shapes. The remaining splines had reasonable hazard profile fits but were not notably improved compared with the standard models (CS Appendix Figure 105−107).
Clinical plausibility	• Clinical experts supported the two-piece log-normal curve as most clinically plausible and representative of expectations. • However, given the late cut-point of two-piece curves, standard models were reassessed using the insights from the advisory board and TA963. Standard log-logistic was very highly concordant to two-piece log-normal in terms of long-term landmark estimates and had good visual fit to the observed KM and hazard plots over time. It was therefore preferred over 2P log-normal to avoid additional complexity, and 2P log-normal was explored in a scenario analysis.
Selected	Base case: • **Standard log-logistic** Scenarios: • Two-piece log-normal

Table 14. Landmark OS estimates, CT: pMMR

Estimates	**Years**			
	2	**5**	**10**	**20**
MSD Clinical Experts – pMMR	50%	15%	5%	NR
Standard parametric models (KEYNOTE-868 [NRG-GY018])				
Exponential	*61%*	*29%*	*8%*	*1%*
Weibull	56%	9%	0%	0%
Log-normal	*57%*	*24%*	*8%*	*2%*
Log-logistic	56%	20%	7%	2%
Gompertz	*58%*	*2%*	*0%*	*0%*
Gamma	**56%**	**13%**	**1%**	**0%**
Generalized Gamma	56%	17%	2%	0%
Spline models (KEYNOTE-868 [NRG-GY018])				
Hazard, k=1	56%	14%	1%	0%
Normal, k=1	56%	19%	5%	1%
Odds, k=1	56%	21%	7%	2%
Hazard, k=2	*57%*	*12%*	*0%*	*0%*
Normal, k=2	56%	17%	3%	0%
Odds, k=2	56%	17%	5%	1%
Hazard, k=3	*57%*	*12%*	*0%*	*0%*
Normal, k=3	56%	15%	3%	0%

Odds, k=3	56%	17%	5%	1%

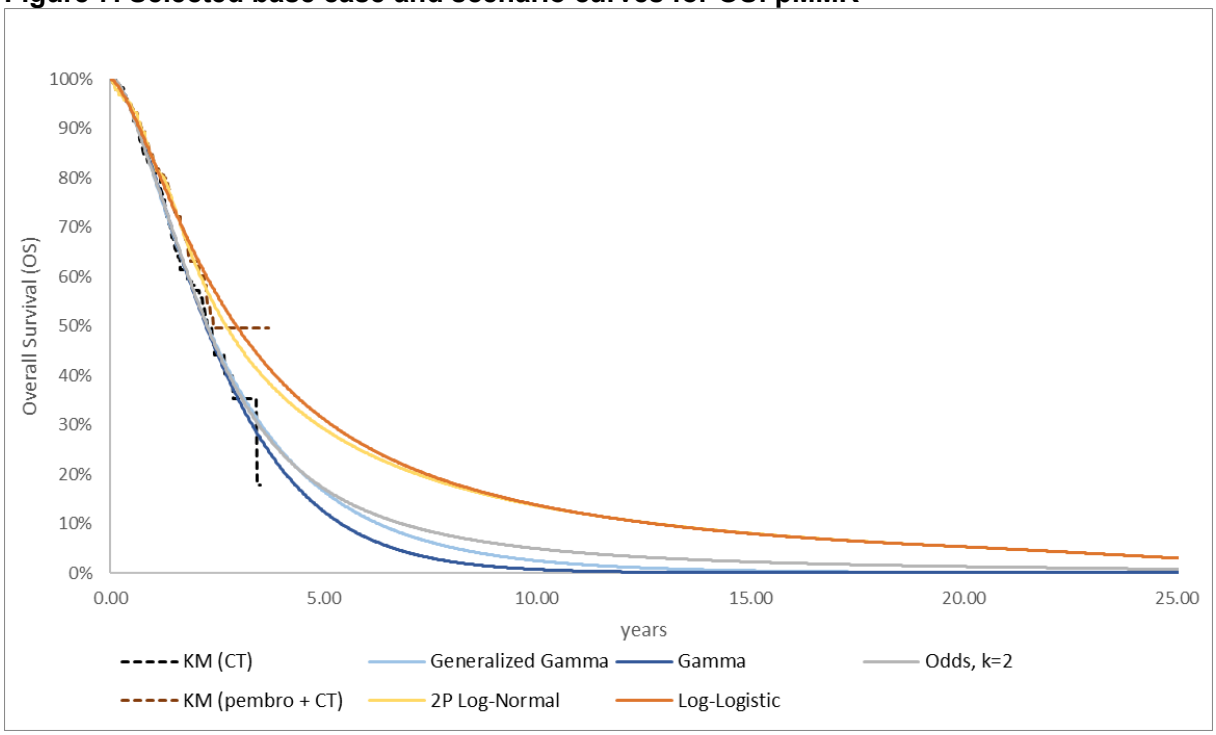
Landmark estimates adjusted for background mortality.
Model in bold selected for the base case.
*Models in *grey italics* excluded due to clinical implausibility based on clinical experts' estimates.

Table 15. Landmark OS estimates, pembrolizumab + CT: pMMR

Estimates	Years			
	2	5	10	20
MSD Clinical Experts – pMMR CT (lower bound)	50%	15%	5%	NR
Standard parametric models (KEYNOTE-868 [NRG-GY018])				
Exponential	67%	36%	13%	2%
Weibull	*64%*	*22%*	*2%*	*0%*
Log-normal	66%	40%	22%	10%
Log-logistic	**64%**	**31%**	**14%**	**5%**
Gompertz	*65%*	*12%*	*0%*	*0%*
Gamma	*65%*	*25%*	*4%*	*0%*
Generalized Gamma	*64%*	*21%*	*2%*	*0%*
Spline models (KEYNOTE-868 [NRG-GY018])				
Hazard, k=1	*64%*	*19%*	*1%*	*0%*
Normal, k=1	64%	28%	10%	2%
Odds, k=1	63%	26%	10%	3%
Hazard, k=2	*64%*	*23%*	*3%*	*0%*
Normal, k=2	64%	26%	9%	2%
Odds, k=2	63%	27%	10%	3%
Hazard, k=3	*64%*	*24%*	*3%*	*0%*
Normal, k=3	64%	25%	7%	1%
Odds, k=3	64%	26%	10%	3%

Landmark estimates adjusted for background mortality.
Model in bold selected for the base case.
*Models in *grey italics* excluded due to clinical implausibility based on clinical experts' estimates.

Figure 7. Selected base case and scenario curves for OS: pMMR



2.2 Results

2.2.1 Deterministic base case results

Table 16. Deterministic base case results: pMMR

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Pembrolizumab + CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.18	[redacted]
CT	[redacted]	2.55	[redacted]	-	-	-	-

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

2.2.2 Probabilistic results

Table 17. Mean probabilistic base case results: pMMR

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Pembrolizumab + CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.14	[redacted]
CT	[redacted]	2.55	[redacted]	-	-	-	-

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Figure 8. Cost effectiveness plane, pembrolizumab + CT versus CT: pMMR

[redacted]

Figure 9. Cost effectiveness acceptability curve, pembrolizumab + CT versus CT: pMMR

[redacted]

2.2.3 Deterministic sensitivity analysis

Figure 10. Tornado diagram, top 10 parameters: pMMR

[redacted]

2.2.4 Scenario analyses

Table 18. Scenario analyses: pMMR

#	Category	Base case value	Scenario value	Rationale	Inc. Costs	Inc. QALYs	ICER	% change
-	**Base case**				[redacted]	**1.18**	[redacted]	
1	Time horizon	35	10	Estimating impact if a shorter time-horizon is selected	[redacted]	0.77	[redacted]	44%
2		35	20		[redacted]	1.10	[redacted]	5%
3	Discount rate (costs and utilities)	3.5%	1.5%	As per NICE guidance	[redacted]	1.42	[redacted]	-14%
4	Impact of AE (cost and disutilities)	Include	Exclude	Remove potential double counting of impact of AEs	[redacted]	1.18	[redacted]	-1%
5	Utility values	KN-158	KN-826 TTD	Explore a wide range of utility sources given that trial-based EQ-5D was not available from KEYNOTE-868 (NRG-GY018)	[redacted]	1.24	[redacted]	-5%
6		KN-158	KN-826 progression-based		[redacted]	1.16	[redacted]	2%
7		KN-158	KN-775 (Swedish value set)		[redacted]	1.39	[redacted]	-15%
8		KN-158	KN-775 (Australian value set)		[redacted]	1.19	[redacted]	-1%
9	Subsequent treatment	Re-weighted trial-based treatment mix based on UK clinician inputs	Per KEYNOTE-868 (NRG-GY018)	Understand the impact of using different subsequent treatment composition in the UK, including IO	[redacted]	1.18	[redacted]	16%

#	Category	Base case value	Scenario value	Rationale	Inc. Costs	Inc. QALYs	ICER	% change
10	Subsequent treatment (CT): dostarlimab	Dostarlimab: 0.00%	Dostarlimab takes pembrolizumab monotherapy share	Estimate impact of a scenario where dostarlimab becomes standard of care for 2L	[redacted]	1.18	[redacted]	0%
11	Healthcare resource utilisation	UK clinician inputs	Healthcare resource use reported in TA963	Estimate impact of a different healthcare resource utilisation pattern	[redacted]	1.18	[redacted]	7%
12	OS extrapolation	Pembrolizumab + CT: Log-logistic CT: Gamma	Pembro + CT: Log-logistic CT: **Gen gamma**	Gen gamma had slightly raised tail vs gamma, exploring comment from clinical expert	[redacted]	1.03	[redacted]	14%
13			Pembro + CT: Log-logistic CT: **2-knot odds**	2-knot odds had slightly further raised tail vs gamma or gen gamma, whilst still broadly consistent with experts' preferences	[redacted]	0.89	[redacted]	29%
14			Pembro + CT: **2P log-normal** CT: Gamma	Two-piece counterpart of the standard log-logistic	[redacted]	1.10	[redacted]	6%
15	PFS extrapolation	Pembro + CT: 2P gen gamma CT: 1-knot odds	Pembro + CT: **2P Weibull** CT: 1-knot odds	2P Weibull also considered suitable by clinical experts, more optimistic estimate	[redacted]	1.17	[redacted]	2%
16		Pembro + CT: 2P gen gamma CT: 1-knot odds	Pembro + CT: **2-knot normal** CT: 1-knot odds	Modest long-term estimates between 2P log-normal and 2P gen gamma, more conservative estimate	[redacted]	1.19	[redacted]	-1%
17	Treatment waning	No waning	Applied to 27.7% of pembrolizumab + CT pMMR patients. Assumed start at 7 years (post treatment initiation) for 2	In accordance with previous IO therapies in endometrial cancer, waning is applied to patients who did not have an ORR. It is applied from 7 years based on the long-term follow-up reported in KEYNOTE-006	[redacted]	1.06	[redacted]	10%

#	Category	Base case value	Scenario value	Rationale	Inc. Costs	Inc. QALYs	ICER	% change
			years before effect of CT is assumed	where no evidence of treatment effect waning is observed.				

Key: 2L, second-line; AE, adverse event; CT, paclitaxel + carboplatin; IO, immunotherapy; ICER, incremental cost effectiveness ratio; ITT, intention to treat; KM, Kaplan–Meier; NICE, National Institute of Health and Care Excellence; OS, overall survival; PFS, progression-free survival; TOT, time on treatment; TTD, time to treatment discontinuation

External Assessment Group's supplementary report for pembrolizumab with platinum-based chemotherapy then pembrolizumab maintenance for treating advanced or recurrent endometrial cancer [ID6381] – Subgroup analyses

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Contributions of authors
Mandy Maredza provided oversight of the critique of the cost-effectiveness evidence and EAG's modelling for the subgroup analyses. Mubarak Patel critiqued the statistical analysis. Aziza Osman and Christiana Anyebe critiqued the cost-effectiveness evidence for each of the subgroups. Naila Dracup provided information specialist support with citations. Sarah Kitson provided clinical expertise. Melanie Powell provided clinical expertise. Jo Parsons coordinated the project and commented on draft versions of the report. All authors contributed to the writing and editing of the report.

Please note that: Sections highlighted in [redacted] are '[redacted]. Sections highlighted in [redacted]. Figures that are CIC have been bordered with blue. [redacted] is highlighted in pink.

1 Background

This document presents the deterministic base case and probabilistic sensitivity analysis (PSA) results separately for the dMMR and pMMR subgroups and supplements the EAG's post-factual accuracy check (FAC) report. Except for survival extrapolations critique presented in detail in this document, and changes to the EAG's chosen starting age in model, all other critiques align with what was previously presented in the EAG's report.

Two accompanying models are provided alongside the document, saved with the EAG's chosen assumptions for the base case as described below for each MMR subgroup (sections 8.1 and 8.2). No modifications to the company's model structure were applied. Exploratory analyses are also presented for treatment waning, health state utilities and resource use.

2 Curve selection and extrapolation

2.1 Modelling approaches

2.1.1 Company

The company provided survival extrapolations and curve selection for the MMR subgroups individually in CS section O.2. Table 59 of appendix O presents the preferred models for the pembrolizumab+CT and CT only arms of KEYNOTE-868 (NRG-GY018) for PFS and OS outcomes across both the dMMR and pMMR subgroups (a total of eight models) with justification for the chosen models. The approach for choosing the models followed a similar methodological approach as the all-comer models in the main company submission document.

These models were fit in a similar manner to the all-comer PFS and OS curves the company provided in the original submission. Parametric, piecewise, and spline models were fit and then assessed for visual fit to the observed KM data and hazards plots, statistical fit using Akaike's information criterion (AIC) and Bayesian information criterion (BIC), and clinical plausibility. In some cases, two-piece models were not considered or preferred due to an already low sample size, mainly in the dMMR subgroup. However, the PFS-CT model in the dMMR subgroup did use a two-

piece model, which begs the question as to why they were not considered for the other three models in the dMMR subgroup outside of the standard parametric models providing “reasonable”, “good”, or “acceptable” visual fit, as the company stated in Table 59.

2.1.2 EAG

In the absence of Kaplan-Meier (KM) IPD, the EAG digitised the PFS and OS plots for the MMR subgroups presented in CS section E.2. and reconstructed pseudo-IPD using the same approach as described in the EAG’s report.

Similar to the company, the EAG selected the most plausible model based on a combination of statistical fit, visual fit, and clinical plausibility. Models with an AIC and/or BIC within five points of the AIC or BIC of the best-fitting model were investigated further for visual fit to the observed KM data and the observed hazard plot, and the EAG’s clinical experts were consulted as to the model with the most plausible survival extrapolations up to 20 years.

Due to time constraints, the EAG first fit and assessed parametric models only. If they were deemed to be a poor fit, then more complicated models such as splines or piecewise models were considered. Additional to the time constraint, due to the low sample size in the dMMR subgroup, piecewise models were not explored in order to maximise sample size in this subgroup.

Table 1 lists the potential models chosen as the EAG’s preferred models for each subgroup, treatment arm, and outcome. In all cases, the potential models were chosen based on good statistical and visual fit to both KM and hazard plots. These potential models were then judged by how plausible the long-term survival extrapolations were compared to the EAG’s clinical experts’ opinions. In cases where multiple models were reasonable and resulted in similar PFS or OS estimates, the simpler of the models were chosen. Table 2 and Table 3 summarise the preferred model choices and the survival extrapolations at key time points by subgroup.

Table 1. EAG's justification for chosen model

Population/outcome	Potential models	Justification
dMMR, CT only, PFS	**Gen Gamma** 2-knot hazards 2-knot normal	Parametric models acceptable visual fit, however pessimistic near KEYNOTE-868 (NRG-GY018) EOS and possibly beyond Spline models better visual fit, more reasonable hazard functions, but much more optimistic over long-term
dMMR, CT only, OS	**Exponential** Log-normal	Parametric and spline models both have reasonable visual fit
dMMR, Pembro + CT, PFS	**Log-logistic** 2-knot normal	Parametric and spline models both have reasonable visual fit, but parametric models looked to be pessimistic beyond KEYNOTE-868 (NRG-GY018)EOS.
dMMR, Pembro + CT, OS	Weibull **Log-logistic** Gamma	Parametric and spline models both have reasonable visual fit
pMMR, CT only, PFS	**2-knot hazards** 2-knot odds 2-knot normal	Parametric models have good visual fit to observed KM data, hazard plots reasonable except the Gompertz model Splines show improved visual fit to data, with reasonable hazards for >1-knot models 2-knot models best fitting
pMMR, CT only, OS	Weibull Log-normal Log-logistic Gamma **1-knot hazards**	Parametric models have decent to good visual fit to observed KM data, hazard plots reasonable except the Gompertz model Spline models fit similarly well
pMMR, Pembro + CT, PFS	**1-knot hazards** 1-knot odds 1-knot normal 2-knot hazards 2-knot odds 2-knot normal	Parametric models too pessimistic near KEYNOTE-868 (NRG-GY018) EOS and beyond Spline models with showing better fit to KM and hazards, with 2-knot models fitting the best visually
pMMR, Pembro + CT, OS	Weibull Log-logistic Gamma 1-knot odds **1-knot normal**	Parametric models have acceptable fit to observed KM data with reasonable hazards except for the Gompertz model Odds and normal spline models fit well
Chosen model denoted in **bold**		

2.2 Summary – curve selection and survival extrapolations

2.2.1 Selected models

Table 2. Summary of the preferred model by company and EAG

Subgroup	Treatment	Outcome	Company	EAG
dMMR	CT only	PFS	Two-piece gamma with 27-week cut	Generalised gamma
		OS	Exponential	Exponential
	Pembrolizumab + CT	PFS	Generalised gamma	Log-logistic
		OS	Log-logistic	Log-logistic
pMMR	CT only	PFS	1-knot odds spline	2-knot hazards
		OS	Gamma	1-knot hazards
	Pembrolizumab + CT	PFS	37-week two-piece generalised gamma	1-knot hazards
		OS	Log-logistic	1-knot normal

2.2.2 Survival extrapolations

Table 3. Survival extrapolations at key timepoints (%)

Model	**2Y**	**5Y**	**10Y**	**20Y**	**Model**	**2Y**	**5Y**	**10Y**	**20Y**
Cycle	**104**	**260**	**520**	**1040**	**Cycle**	**104**	**260**	**520**	**1040**
dMMR; CT only; PFS					**pMMR; CT only; PFS**				
Company	[redacted]				Company	[redacted]			
EAG	[redacted]				EAG	[redacted]			
dMMR; CT only; OS					**pMMR; CT only; OS**				
Company	72	44	19	4	Company	56	13	1	0
EAG	72	44	19	4	EAG	56	14	1	0
dMMR; Pembrolizumab + CT; PFS					**pMMR; Pembrolizumab + CT; PFS**				
Company	[redacted]				Company	[redacted]			
EAG	[redacted]				EAG	[redacted]			
dMMR; Pembrolizumab + CT; OS					**pMMR; Pembrolizumab + CT; OS**				

Company	83	64	42	25	Company	64	31	14	5
EAG	83	64	42	25	EAG	64	28	10	2
Survival extrapolations for both company and EAG retrieved from the company's economic model									

3 Population

In the main report, the EAG proposed a different baseline starting age for the model in the all-comer population based on the EAG's clinical expert advice and external evidence reviewed. However, post AC1, the EAG received CDF data on baseline characteristics (age) of endometrial cancer patients who receive immunotherapy (summarised in Table 4). The data on advanced/ metastatic endometrial cancer patients (previously untreated in advanced setting) who receive dostarlimab plus chemotherapy appears most relevant to the decision problem. Both the population (untreated in advanced setting) and intervention (immunotherapy plus CT) are more closely aligned to the current appraisal with the caveat that it is only for dMMR patients. That data indicates that the company's current chosen values for age in dMMR patients (65.7 years) aligns closely to that reported for patients receiving dostarlimab+CT. Thus, the EAG believes that the company's values used in model and obtained in KEYNOTE-868 (NRG-GY018) are likely a close reflection of starting ages observed in practice. Since that data is specifically for pembrolizumb plus chemotherapy, it appears more reasonable to maintain the current values in model for both dMMR and pMMR.

Table 4: Overview of CDF data on patients with endometrial cancer having immunotherapy

Immunotherapy	Median/ Mean age (yrs)	Population	EAG comments
Pembrolizumab plus lenvatinib (PEMB23)	Mean age – 67.5 Median - 69	Patients previously treated with platinum-containing therapy given in any setting (neoadjuvant, adjuvant, chemo-radiotherapy, 1L for	Reports on previously treated population. Does not align with current appraisal

Immunotherapy	Median/ Mean age (yrs)	Population	EAG comments
		advanced/metastatic disease)	
Dostarlimab monotherapy (DOS 1)	Mean -66 Median 67	Patients with advanced/ metastatic dMMR endometrial cancer previously treated in the advanced/metastatic disease setting with chemotherapy	Reports on a previously treated population
Dostarlimab plus chemotherapy (DOS 2)[1]	Mean – 65.4 Median -66	Patients with advanced/ metastatic dMMR endometrial cancer previously untreated in the advanced/metastatic disease setting	Immunotherapy plus CT and in previously untreated advanced setting therefore more closely aligns with current appraisal. Caveat: dMMR population only
Dostarlimab plus chemotherapy (DOS 2 – excluding EAMS/Post-EAMS)	Mean – 65.58 Median -67	Patients with advanced/ metastatic dMMR endometrial cancer previously untreated in the advanced/metastatic disease setting	Immunotherapy plus CT and in previously untreated advanced setting therefore more closely aligns with current appraisal. Caveat: dMMR population only

[1] This includes 60 Early Access to Medicines Scheme (EAMS) and post-EAMS approvals

4 Health-related quality of life

As with the all-comer population analysis, for the subgroup analysis, the company relied on health state utilities from KEYNOTE-158 based on patients with MSI-H/dMMR endometrial cancer who had previously failed standard therapy. Utility values of [redacted] and [redacted] were applied to the progression-free and progressed disease health states respectively. A one-off QALY decrement associated with grade

3+ AEs with an incidence of >5% in the trial was applied in the first cycle of the model for each intervention arm. For the dMMR subgroup, the utility decrement was -[redacted] for patients in the Pembrolizumab +CT arm versus -[redacted] for patients in the CT arm. In the pMMR subgroup, a utility decrement of -[redacted] was estimated for patients in the Pembrolizumab +CT arm and -[redacted] for patients in the CT arm. The utility estimates were adjusted by age to account for the natural decline in QoL using the general female population utility values from Hernández Alava et al.[1] The base-case health-state utilities and adverse event disutilities applied in the economic model are presented in Table 5 and Table 6 below.

Table 5: EQ-5D-3L values used in CEM

Health state	(N=[redacted]) Mean (SE)	95% CI	Source
Progression-free	[redacted]	[redacted]	KEYNOTE-158
Progressed	[redacted]	[redacted]	KEYNOTE-158

Source: Table 42, **pg.130, CS document B**

Table 6: Adverse event disutilities used in CEM

Adverse Event	Disutility	Source (disutility)
Neutrophil count decreased	0.00	Assumed to have no utility impact, as per NICE TA963
White blood cell count decreased	0.00	Assumed to have no utility impact, as per NICE TA963
Lymphocyte count decreased	0.00	Assumed to have no utility impact, as per NICE TA963
Hypertension	-0.020	NICE TA963
Anaemia	-0.119	NICE TA963

Source: Table 46, **pg.137, CS document B**

In line with the all-comer population analysis, the company estimated utilities from a range of different sources to explore the impact on the ICER, given that there was no EQ-5D data available from KEYNOTE-868 (NRG-GY018). These scenarios included using TTD and progression-based utilities from KEYNOTE-826 and progression-based utilities from KEYNOTE-775 based on the Swedish and Australian value set.

On pg. 128 CS Document B, the company states that utility values from KEYNOTE-775 based on the UK value set could not be disclosed for the purpose of this appraisal due to contractual obligations with a third party. KEYNOTE-826 assessed pembrolizumab + CT versus CT as 1L therapy in treating patients with untreated persistent, recurrent or metastatic cervical cancer. KEYNOTE-775 examined the use of pembrolizumab in combination with lenvatinib for previously treated advanced EC. The utilities used in the scenario analyses are presented in Table 7.

Table 7: Summary of utility values for scenario analyses

Source	State	Utility value: mean (SE)	Reference
Time-to-death utilities	360+ days	[redacted]	KEYNOTE-826
	180-359 days	[redacted]	
	90-179 days	[redacted]	
	30-89 days	[redacted]	
	<30 days	[redacted]	
Progression-based utilities	Progression-free	[redacted]	
	Progressed	[redacted]	
	Progression-free	0.736	PBAC_Pembrolizumab 2022/KEYNOTE-775
	Progressed	0.700	
	Progression-free	0.851	Ralph 2024/KEYNOTE-775
	Progressed	0.817	

Source: Table 48, pg.139, CS document B

EAG comments:

The EAG maintains that the health state utilities used in economic model may not be representative of patients with pMMR given the trial only recruited MSI-H/dMMR endometrial cancer patients. Clinical advice to the EAG suggests that there could be differences in the HRQoL of pMMR and dMMR cohort, as there is a *higher response rate to treatment with dMMR and they will likely be on treatment for longer*. In addition, *pMMR endometrial cancer does not respond as well to immunotherapy so one might assume that this cohort will have a less good quality of life as they are more likely to have active/progressive disease*. This is supported by clinical advice in TA904, which indicates that "*dMMR tumours are generally (but not always)*

considered to have a better treatment response and prognosis than pMMR tumours, and most importantly are more likely to respond to immunotherapy.[2] Previous clinical trials have shown that immunotherapies have limited efficacy in the pMMR population, with higher ORRs observed in dMMR compared to pMMR patients[3-5] This uncertainty remains unresolved due to a lack of data available from the pivotal trial, as well as the literature on patients with pMMR endometrial cancer.

5 Treatment waning

In the subgroup analysis, no treatment waning was assumed in the base-case analysis. A scenario assuming gradual treatment waning in the OS curve was applied to 24.8% of patients who did not attain ORR. In accordance with KEYNOTE-006, treatment waning was assumed to start 7 years after starting treatment (or five years post-discontinuation). The EAG maintains its previous position that due to the trial's short follow-up, there is insufficient evidence to support that treatment effect is sustained for such a long period. Previous NICE committees on immunotherapy appraisals have excepted more pessimistic treatment waning assumptions of three to five years post-discontinuation.[6-8]

6 Resource use and costs

6.1 Intervention and comparators' costs and resource use

The primary treatment costs calculated for Pembrolizumab + CT, and Placebo + CT from the drug acquisition costs and the administration costs have been explained explicitly in the EAG report. All assumptions made for the all-comer population applies to the dMMR and pMMR subgroups considered in the KEYNOTE-868 (NRG-GY018) trial. The EAG has considered the assumptions to be appropriate.

6.2 Health state resource use and costs

The costs of managing the disease, monitoring and following up the patients in the health states were estimated in the model for the pMMR and the dMMR subgroups. The resource use was assumed to differ between the PFS (progression free state) and the PD (progressed disease) state and based on treatment status. The

assumptions used for the frequency of resource used by patients were obtained by consulting clinical experts, advisory board and through HTA search of similar cancers. On consultation with the EAG clinical experts, the resource used by the CS was thought to be underestimated for the Pembrolizumab + CT arm as the expert advised that EC patients on immunotherapy undergo series of blood tests (details of this can be found in the EAG report). The EAG presents its preferred assumptions, based on consultation with clinical experts and sourcing from TA963, in Table 8. These values are the same for both subgroups as the resource use is determined by patient health states and treatment status. Table 9 presents the company's values for MMR subgroups resource use, which are the same for the all-comer analysis. All unit costs were sourced from NHS reference costs 2022/23 and are presented in the EAG report, Table 23.

Table 8: Resource use for Pembrolizumab + CT arm obtained by the EAG

Health state	Resource	Frequency per week	source	Frequency per week	source
		Scenario 1		**Scenario 2**	
PFS (on treatment)	Blood tests	0.33 (up to cycle 17) 0.17 (cycle 18+)	EAG clinical expert	0.33 (up to cycle 18) 0.22 (cycle 19+)	TA963
	Outpatient visits	0.33 (up to cycle 17) 0.17 (cycle 18+)	EAG clinical expert	0.30 (up to cycle 18) 0.13 (cycle19+)	TA963
PFS (off treatment)	Blood tests	0.08	EAG clinical expert	0.17	Company base case
	Outpatient visits	0.08	EAG clinical expert	0.06	Company base case

Table 9: Heath state resource use for the pMMR and dMMR Subgoups (Company's assumptions)

Health state	Resource	Frequency per week		Source
		pMMR	**dMMR**	
PFS (on treatment) pembrolizumab + CT	Ct scan	0.08	0.08	Advisory board
	Outpatient visits	0.17	0.17	Advisory board
	Blood test	0.17	0.17	Advisory board
PFS (off treatment) pembrolizumab + CT	Ct scan	0.08	0.08	Advisory board
	Outpatient visit	0.06	0.06	Advisory board
	Blood test	0.17	0.17	Advisory board
PFS (On treatment): CT	Ct scan	0.09	0.09	Advisory board

	Outpatient visits	0.29	0.29	Advisory board
	Blood test	0.29	0.29	Advisory board
PFS (Off treatment): CT	Ct scan	0.08	0.08	Advisory board
	Outpatient	0.06	0.06	Advisory board
	Blood test	0.00	0.00	Advisory board
PD	Ct scan	0.04	0.04	Advisory board
	Outpatient visit	0.11	0.11	Advisory board
	Blood test	0.11	0.11	Advisory board
Source: CS model, worksheets disease management costs in PFS and PD				

pMMR, mismatch repair proficient; dMMR, mismatch repair deficient; CT, chemotherapy; Ct, computed tomography; PFS, progression-free state; PD, progressed disease

6.3Costs of subsequent treatments

The subsequent treatment costs were estimated per patient by considering the proportion of patients receiving subsequent treatment, average time on treatment, the distribution of each subsequent treatment, and drug acquisition and administration costs of each therapy. These costs were calculated as a one-off cost upon entry into the PD state in the economic model. The same approach was taken for obtaining the proportion of patients on subsequent treatment as described for the all-comer population. Data obtained from the KEYNOTE-868 (NRG-GY018) trial were adjusted and validated to reflect UK clinical practice.

The proportions of patients receiving subsequent treatments in the pMMR and dMMR alongside the all-comer population are presented in Table 10. The dosage and costs per week of subsequent treatments are the same for the all-comer population and presented in Table 20 of the EAG report. All the assumptions surrounding the proportion of subsequent treatment are deemed appropriate by the EAG.

Table 10: Subsequent treatment mix for the for the pMMR and dMMR subgoups

Subsequent treatment	**ALL-comer population**	**pMMR**	**dMMR**
Pembrolizumab +CT arm			
Carboplatin	1.65%	0.00%	8.93%
Carboplatin + paclitaxel	14.31%	11.50%	26.79%
Doxorubicin	13.69%	14.78%	8.93%
Letrozole	7.31%	4.93%	17.86%
Megestrol	0.00%	0.00%	0.00%

Paclitaxel	8.27%	10.14%	0.00%
Pembrolizumab	0.00%	0.00%	0.00%
Pembrolizumab + Lenvatinib	0.00%	0.00%	0.00%
Radiotherapy	23.06%	26.28%	8.93%
No active treatment	31.72%	32.37%	28.57%
CT arm			
Carboplatin	1.84%	2.50%	0.00%
Carboplatin + paclitaxel	11.34%	14.17%	3.51%
Doxorubicin	1.22%	1.67%	0.00%
Letrozole	4.60%	5.00%	3.51%
Megestrol	1.84%	2.50%	0.00%
Paclitaxel	8.98%	12.22%	0.00%
Pembrolizumab	16.76%	0.00%	63.10%
Pembrolizumab + Lenvatinib	23.95%	32.59%	0.00%
Radiotherapy	11.68%	10.83%	14.02%
No active treatment	17.78%	18.52%	15.87%
Source: CS economic model, subsequent treatment worksheet			

pMMR, mismatch repair proficient; dMMR, mismatch repair deficient; CT, chemotherapy

6.4 Treatment of adverse events costs

The costs of adverse events were estimated as a one-off cost in the first model cycle as the product of the rate of AE per subject, number of episodes of AEs per subject, and the unit cost of the AE. The assumptions for estimating the costs of adverse events are considered appropriate by the EAG. In its report, the EAG indicated that immune-related AEs (irAEs) reported in ≥ 2% of the trial's all-comer population are toxicities that need clinical management, and their exclusion likely underestimates costs of AEs. Whilst the EAG maintains this argument, the inclusion of AEs of grade 3+ occurring in ≥ 2% in the EAG's exploratory analysis for the all-comer population yielded only a minimal change to the company base case ICER. But it is worth noting that only neutropenia and anaemia were costed in the model for the two subgroups, although hypertension was listed in the AEs occurring in ≥ 5% as seen in table 12 and neutropenia was not. The EAG questions the exclusion of hypertension and inclusion of neutropenia. However, there seems to be an apparent mismatch between the values reported in table 12, and those in the model. The model values indicate that neutropenia and anaemia are the two AEs with cost attached that occurred in ≥ 5% of patients and Hypokalaemia ([redacted] of dMMR patients) had no cost. The impact on the company's base case ICER was negligible when hypertension was used instead of neutropenia and when hypokalaemia was costed for the dMMR

subgroup. Table 11 presents the AEs included in the subgroup analyses as implemented in the economic model and Table 12 shows the proportion of patients with grade 3+ AEs in the subgroups.

Table 11: Adverse events costs for pMMR and dMMR subgroups applied in the model

Adverse events	Cost per episode (£)	Source
Lymphocyte count decreased	0.00	Assumed no cost
White blood cell counts decreased	0.00	NICE TA904
Neutrophil count decreased	0.00	NICE TA904
Neutropenia	1,667.58	NHS Reference costs 2022/23
Anaemia	565.40	NHS Reference costs 2022/23
Source: CS B Table 57 and Model, adverse events costs worksheet		

Table 12: Adverse events of grade 3+ occurring in ≥ 5% of patients in pMMR and dMMR cohorts

Adverse events	**pMMR**	**dMMR**
Pembrolizumab + CT arm		
Neutrophil count decreased	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]
Lymphocyte count decreased	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
CT arm		
Neutrophil count decreased	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]
Lymphocyte count decreased	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Source: Table 57 CS Appendix O, pg.183		

pMMR, mismatch repair proficient; dMMR, mismatch repair deficient; CT, chemotherapy

7 EAG summary and critique of resource use and cost

The EAG considers the resource use, cost assumptions, and their integration into the MMR subgroup cohorts' economic model appropriate. Resource allocation for the pembrolizumab +CT arm remains the EAG's main concern as detailed in the EAG report. Another area of concern with minimal impact on ICER is the exclusion of hypertension from AE costs despite meeting the established criteria. However, it is likely that there was an error in reporting of AEs in Table 12 as explained above.

8 Cost-effectiveness results

8.1 dMMR subgroup

The EAG's adjustments to the company's base case model are presented in Table 13, showing the individual effect of each change as well as the combined effect of all changes cumulatively for dMMR subgroup. Table 14 and Table 15 show the EAG's estimated deterministic and probabilistic ICERs respectively.

The EAG's deterministic ICER for the dMMR subgroup was [redacted], representing a 6% increase from the company's base case ICER. The most influential adjustment was the EAG clinical experts' resource use assumption, followed by the selection of the standard log-logistic model for PFS extrapolation in the pembrolizumab + CT arm. The probabilistic ICER was [redacted].

Table 13: EAG preferred model assumptions, dMMR

Preferred assumption	Section in EAG report	ICER £/QALY (Individual impact on company base case ICER)	Percentage change in ICER
Company base-case		[redacted]	

Preferred assumption	Section in EAG report	ICER £/QALY (Individual impact on company base case ICER)	Percentage change in ICER
EAG 01: Generalised gamma model for PFS extrapolation; CT only	2.2.1	[redacted]	[redacted]
EAG 02: Log-logistic model for PFS extrapolation; Pembrolizumab + CT	2.2.1	[redacted]	[redacted]
EAG 03: Resource utilisation to reflect EAG clinical experts' opinion PFS (on treatment): Blood test – 0.33 (up to cycle 17), 0.17 (cycle 18+); Outpatient visits – 0.33 (up to cycle 17), 0.17 (cycle 18+) PFS (off treatment): Blood tests – 0.08; Outpatient visits – 0.08	5.2	[redacted]	[redacted]
EAG Base Case (Applied all changes cumulatively)		[redacted]	[redacted]

Table 14: EAG deterministic base case cost-effectiveness analysis (with PAS price used for pembrolizumab), dMMR

Technologies	Total Costs (£)	LYG	QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
CT	[redacted]	5.01	[redacted]				
Pembrolizumab + CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2.10	[redacted]

Table 15: EAG probabilistic base case cost-effectiveness analysis (with PAS price used for pembrolizumab), dMMR

Technologies	Total Costs (£)	LYG	QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
CT	[redacted]	4.99	[redacted]				
Pembrolizumab + CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.84	[redacted]

The results from the probabilistic sensitivity analysis are plotted in the cost-effectiveness acceptability curve and cost-effectiveness plane below (Figure 1 and Figure 2). At willingness-to-pay thresholds of £20,000 and £30,000, pembrolizumab + CT has a probability of being cost-effective compared to CT alone of [redacted] and [redacted] respectively.

Figure 1 Cost-effectiveness acceptability curve, EAG base case, dMMR

Figure 2 Cost-effectiveness plane, EAG base case, dMMR

8.1.1 EAG exploratory analyses dMMR

The exploratory analyses undertaken by the EAG for dMMR subgroup are presented in Table 16.

Table 16: EAG exploratory analyses, dMMR

Parameter varied	Base case value	Scenario value	Rationale	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Percentage change in ICER
MSD base case (post clarifications)				[redacted]	2.12	[redacted]	[redacted]
Treatment waning in OS	No treatment waning assumed	**Scenario 1** 3 years after discontinuing pembrolizumab + CT	Precedent in previous NICE appraisals where patients discontinue treatment with immunotherapy after two years	[redacted]	1.88	[redacted]	[redacted]
		Scenario 2 4 years after discontinuing pembrolizumab + CT		[redacted]	1.92	[redacted]	[redacted]
HSU from McCarthy et al 2024	PFS: [redacted] PD: [redacted]	**PFS:** 0.72 **PD:** 0.67	Utilities were estimated based on progression status and tumour site data from KEYNOTE-158 using a UK value set.	[redacted]	2.11	[redacted]	[redacted]
Resource use frequency per week of blood tests and outpatient visits in the pembrolizumab + CT arm	PFS (on treatment): Blood tests - 0.17, outpatient visits - 0.17 PFS (off treatment) - Bood test – 0.17	**Scenario 1** PFS (on treatment): Blood test – 0.33 (up to cycle 17), 0.17 (cycle 18+) Outpatient visits – 0.33 (up to	EAG Clinical experts most appropriate estimates.	[redacted]	2.12	[redacted]	[redacted]

Parameter varied	Base case value	Scenario value	Rationale	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Percentage change in ICER
	Outpatient visits – 0.06	cycle 17), 0.17 (cycle 18+) PFS (off treatment): Blood tests – 0.08 Outpatient visits – 0.08					
		Scenario 2 PFS (on treatment): Blood test – 0.33 (up to cycle 18), 0.22 (cycle 19+) Outpatient visits – 0.30 (up to cycle 18), 0.13 (cycle 19+) PFS (off treatment):	Explore data from TA963 to assess uncertainty.	[redacted]	2.12	[redacted]	[redacted]

Parameter varied	Base case value	Scenario value	Rationale	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Percentage change in ICER
		Blood tests – 0.17 (company's base case) Outpatient visits – 0.06 (company's base case)					

8.2 pMMR subgroup

The EAG's preferred assumptions for pMMR subgroup are presented in Table 17.

Table 17: EAG preferred model assumptions (pMMR cohort)

Preferred assumption	ICER (£/QALY)	Section in EAG report	Impact on company base case
Company base case ICER			
EAG 01: OS extrapolation for Pembrolizumab + CT: 1-knot normal		2.2.1	
EAG 02: OS extrapolation for CT: 1 knot hazards		2.2.1	
EAG 03: PFS extrapolation Pembrolizumab + CT: 1- knot hazards		2.2.1	
EAG 04: PFS extrapolation CT: 2-knot hazards		2.2.1	
EAG 05: Resource use PFS (on-treatment): Blood test - 0.33 (up to cycle 17), 0.17 (cycle 18+). Outpatients visit - 0.33 (up to cycle 17), 0.17 (cycle 18+) PFS (off-treatment): Blood test- 0.08, outpatient visit – 0.08		6.2	
EAG base case (All changes applied)			

Table 18: Deterministic cost-effectiveness results, pMMR (EAG base case)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	INMB (£)
Pembrolizumab + CT	[redacted]	[redacted]	[redacted]	-	-	-	-	-
CT	[redacted]	2.61	[redacted]	[redacted]	[redacted]	0.83	[redacted]	[redacted]

Table 18 above shows the results of the deterministic cost-effectiveness analysis, based on EAG's preferred base case assumptions. The ICER increased from [redacted] (Company's base case) to [redacted] (EAG's base case). The main driver of the increased ICER was the OS extrapolation approach for pembrolizumab +CT.

Table 19:Probabilistic mean cost-effectiveness results, pMMR (EAG base case)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	INMB (£)
Pembrolizumab + CT	[redacted]	[redacted]	[redacted]	-	-	-	-	-
CT	[redacted]	2.67	[redacted]	[redacted]	[redacted]	0.81	[redacted]	[redacted]

Probabilistic sensitivity analysis was performed on the EAG base case using 1000 iterations drawn from parametric assumptions in the adapted economic model for the pMMR subgroup. Incremental costs were [redacted] and incremental QALYs 0.81 resulting in an ICER of [redacted] (Table 19). At a £30,000 WTP threshold pembrolizumab +CT return an iNMB of [redacted] and no iNHB. The cost-effectiveness scatterplot indicates that most iterations lie in the North-East quadrant i.e., Pembrolizumab+CT is both more costly and more effective than CT (Figure 3). While majority of the iterations were in the North-East quadrant, about [redacted] of the points were presented in the North-West quadrant depicting that for those cost and effect pairs, the intervention was more costly and less effective. The cost-effectiveness acceptability curve (CEAC) shows that the probability of pembrolizumab + CT being cost-effective compared to CT at £20,000 WTP threshold was [redacted] and increases to [redacted] at the £30,000 WTP threshold (Figure 4).

Figure 3: Cost effectiveness plane, pembrolizumab + CT versus CT: pMMR (EAG base case)

Figure 4: Cost effectiveness acceptability curve, pembrolizumab + CT versus CT: pMMR (EAG base case)

8.2.1 EAG exploratory analyses pMMR subgroup

Table 20 shows the results of the EAG's exploratory analyses for the pMMR subgroup.

Table 20: EAG Exploratory Analyses, pMMR

Parameter varied	Base case value	Scenario value	Rationale	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Percentage change in ICER
Company base case				[redacted]	1.18	[redacted]	[redacted]
Treatment waning in OS	No treatment waning assumed	**Scenario 1** 3 years after discontinuing pembrolizumab + CT	Precedent in previous NICE appraisals where patients discontinue treatment with immunotherapy after two years	[redacted]	1.04	[redacted]	[redacted]
		Scenario 2 4 years after discontinuing pembrolizumab + CT		[redacted]	1.06	[redacted]	[redacted]
HSU from McCarthy et al 2024	PFS: [redacted] PD: [redacted]	**PFS:** 0.72 **PD:** 0.67	Utilities were estimated based on progression status and tumour site data from KEYNOTE-158	[redacted]	1.15	[redacted]	[redacted]

Parameter varied	Base case value	Scenario value	Rationale	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Percentage change in ICER
			using a UK value set.				
Resource use frequency per week of blood tests and outpatient visits in the pembrolizumab + CT arm	PFS (on treatment): Blood tests - 0.17, outpatient visits - 0.17 PFS (off treatment) - Bood test – 0.17 Outpatient visits – 0.06	**Scenario 1** PFS (on treatment): Blood test – 0.33 (up to cycle 17), 0.17 (cycle 18+) Outpatient visits – 0.33 (up to cycle 17), 0.17 (cycle 18+) PFS (off treatment): Blood tests – 0.08 Outpatient visits – 0.08	EAG Clinical experts most appropriate estimates	[redacted]	1.18	[redacted]	[redacted]
		Scenario 2 PFS (on treatment):	Explore data from TA963 to assess uncertainty	[redacted]	1.18	[redacted]	[redacted]

Parameter varied	Base case value	Scenario value	Rationale	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Percentage change in ICER
		Blood test – 0.33 (up to cycle 18), 0.22 (cycle 19+) Outpatient visits – 0.30 (up to cycle 18), 0.13 (cycle 19+) PFS (off treatment): Blood tests – 0.17 (company's base case) Outpatient visits – 0.06 (company's base case)					

9 Appendices

EAG's modelling figures and tables

dMMR subgroup

CT only (PFS)

Figure 5. Paramedic model fit over trial length (dMMR, CT only, PFS)

Figure 6. Parametric model fit over 20 years (dMMR, CT only, PFS)

Figure 7. Parametric model hazard functions plot (dMMR, CT only, PFS)

Figure 8. Spline model fit over trial length (dMMR, CT only, PFS)

Figure 9. Spline model hazard functions plot (dMMR, CT only, PFS)

Table 21. Statistical model fit (dMMR, CT only, PFS)

Model	AIC	BIC	AIC rank	BIC rank
Exponential	555.9875	558.706		
Weibull	557.2919	562.7289		
Log-normal	536.4445	541.8815		
Log-logistic	538.6191	544.0561		
Gompertz	553.6009	559.0379		
Generalised Gamma	529.4607	537.6162		
Gamma	554.9992	560.4362		
Hazards k=1	**517.6222**	**525.7777**	**Similar**	**Best**
Hazards k=2	517.9625	528.8365	Similar	Similar
Hazards k=3	518.1894	531.7819	Similar	
Odds k=1	518.7822	526.9377	Similar	Similar
Odds k=2	516.7476	527.6216	Similar	Similar
Odds k=3	518.2708	531.8633	Similar	
Normal k=1	524.9321	533.0876		
Normal k=2	**516.4412**	**527.3152**	**Best**	Similar
Normal k=3	518.3485	531.941	Similar	

CT only (OS)

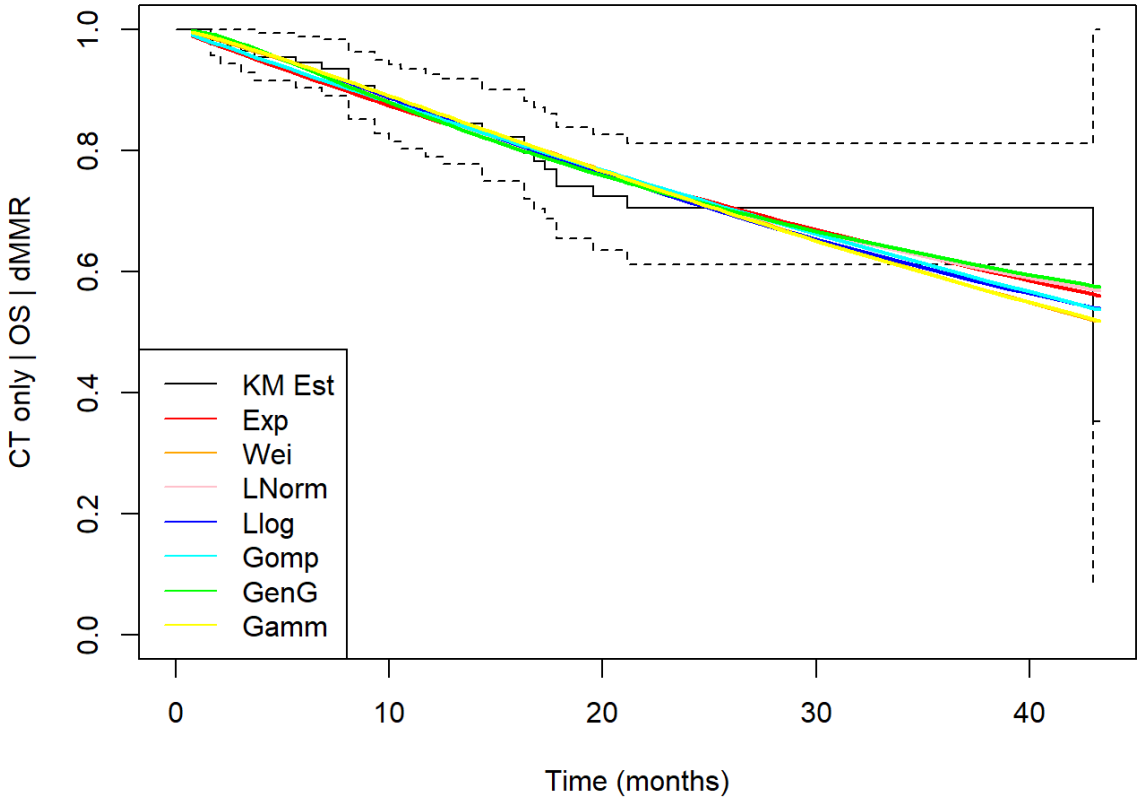

Figure 10. Parametric model fit over trial length (dMMR, CT only, OS)

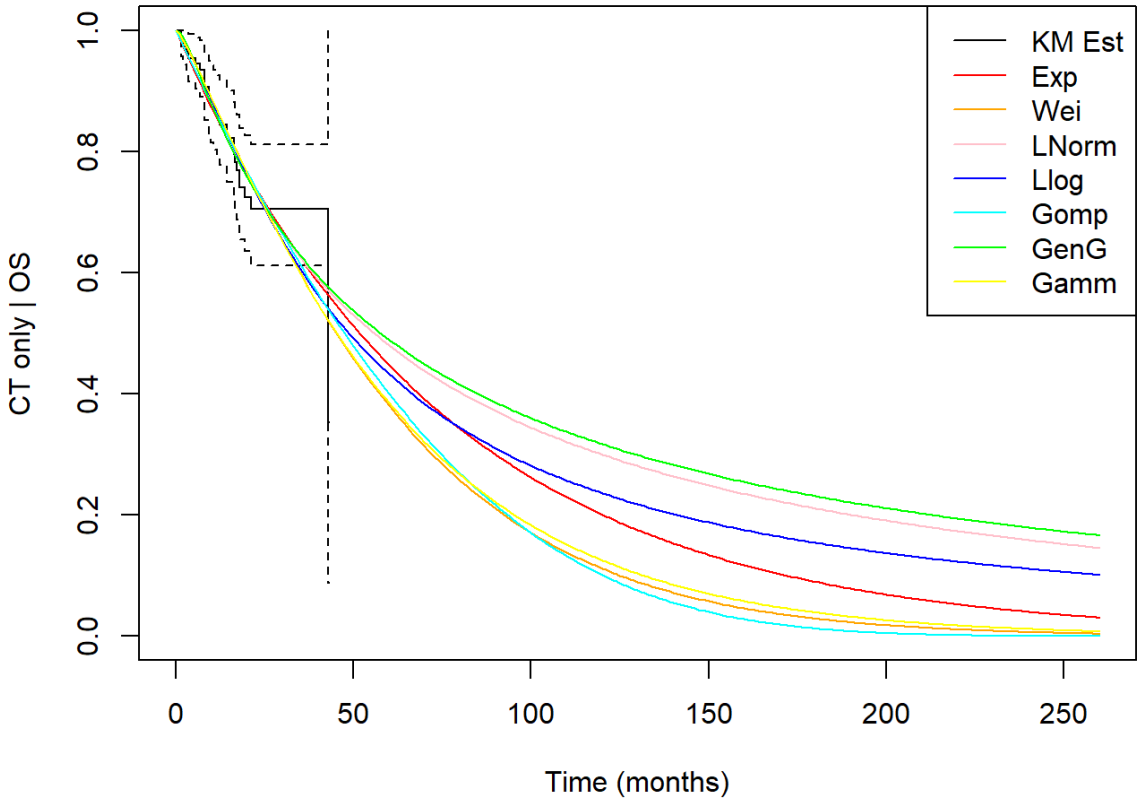

Figure 11. Parametric model fit over 20 years (dMMR, CT only, OS)

Figure 12. Parametric model hazard functions plot (dMMR, CT only, OS)

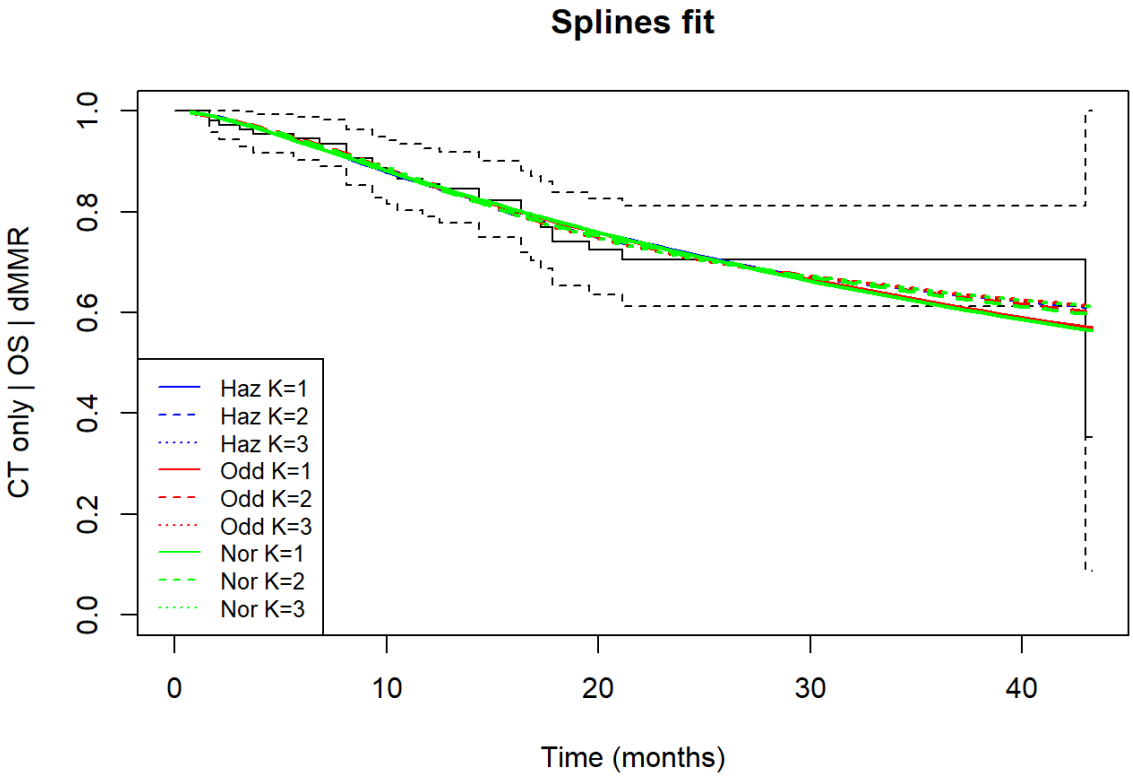

Figure 13. Spline model fit over trial length (dMMR, CT only, OS)

Figure 14. Spline model hazard functions plot (dMMR, CT only, OS)

Table 22. Statistical model fit (dMMR, CT only, OS)

Model	AIC	BIC	AIC rank	BIC rank
Exponential	**288.9639**	**291.6824**	**Similar**	**Best**
Weibull	290.072	295.509	Similar	Similar
Log-normal	**288.7982**	**294.2352**	**Best**	**Similar**
Log-logistic	289.4804	294.9174	Similar	Similar
Gompertz	290.8655	296.3025	Similar	Similar
Generalised Gamma	290.7859	298.9414	Similar	
Gamma	289.8834	295.3204	Similar	Similar
Hazards k=1	291.1063	299.2617	Similar	
Hazards k=2	292.5084	303.3824	Similar	
Hazards k=3	294.3076	307.9001		
Odds k=1	291.0708	299.2263	Similar	
Odds k=2	292.592	303.466	Similar	
Odds k=3	294.3634	307.9559		
Normal k=1	290.7867	298.9422	Similar	
Normal k=2	292.3789	303.2529	Similar	
Normal k=3	294.0693	307.6618		

Pembrolizumab + CT (PFS)

Figure 15. Parametric model fit over trial length (dMMR, Pembro + CT, PFS)

Figure 16. Parametric model fit over 20 years (dMMR, Pembro + CT, PFS)

Figure 17. Parametric model hazard functions plot (dMMR, Pembro + CT, PFS)

Figure 18. Spline model fit over trial length (dMMR, Pembro + CT, PFS)

Figure 19. Spline model hazard function plot (dMMR, Pembro + CT, PFS)

Table 23. Statistical model fit (dMMR, Pembro + CT, PFS)

Model	AIC	BIC	AIC rank	BIC rank
Exponential	**369.3953**	**372.0958**	**Similar**	**Best**
Weibull	370.8737	376.2746	Similar	Similar
Log-normal	368.7523	374.1533	Similar	Similar
Log-logistic	369.0505	374.4515	Similar	Similar
Gompertz	368.0403	373.4413	Similar	Similar
Generalised Gamma	370.7288	378.8302	Similar	
Gamma	371.106	376.507	Similar	Similar
Hazards k=1	370.3773	378.4787	Similar	
Hazards k=2	367.6256	378.4275	Similar	
Hazards k=3	369.5404	383.0428	Similar	

Odds k=1	370.0594	378.1609	Similar	
Odds k=2	367.6017	378.4036	Similar	
Odds k=3	369.5629	383.0653	Similar	
Normal k=1	370.6501	378.7515	Similar	
Normal k=2	**367.582**	**378.3839**	**Best**	
Normal k=3	369.58	383.0824	Similar	

Pembrolizumab + CT (OS)

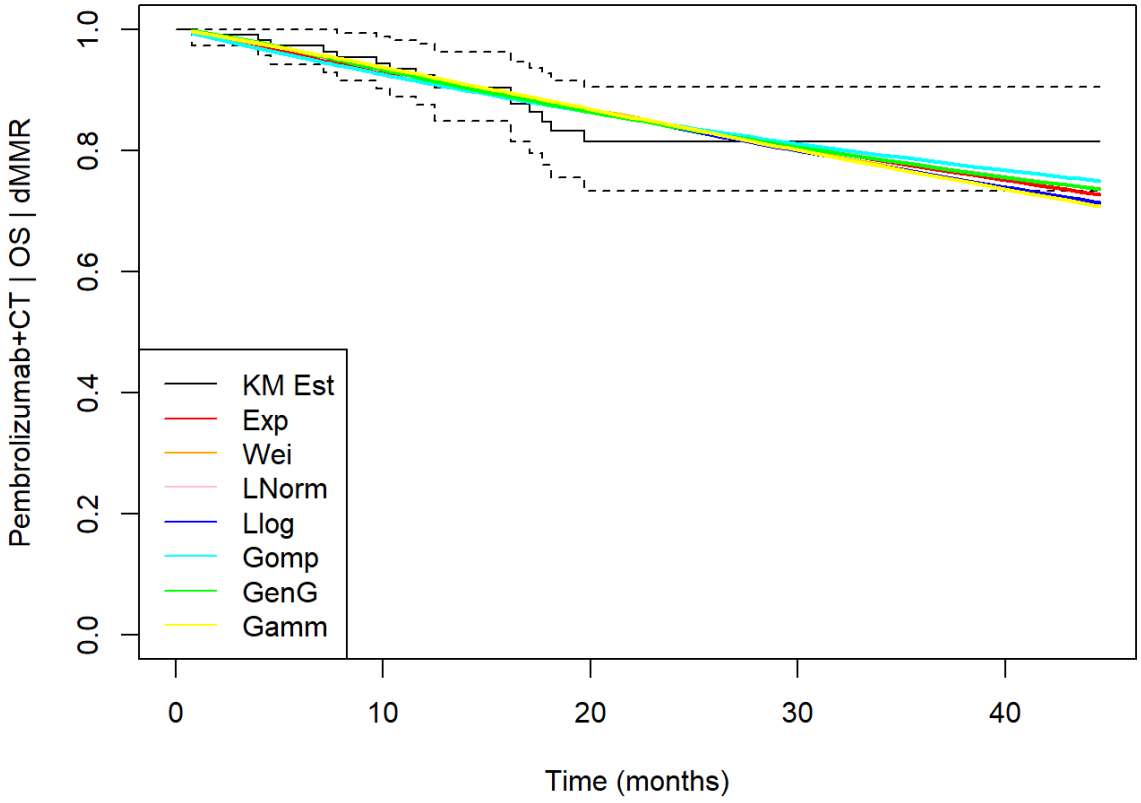

Figure 20. Parametric model fit over trial length (dMMR, Pembro + CT, OS)

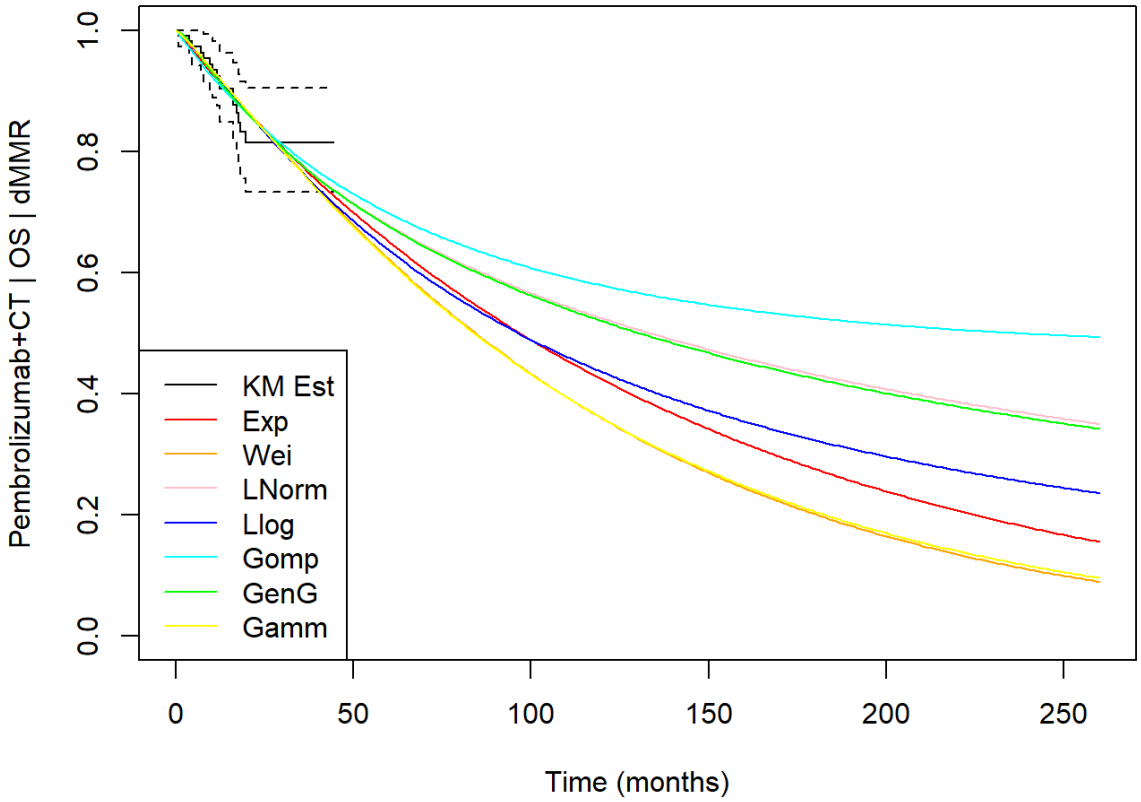

Figure 21. Parametric model fit over 20 years (dMMR, Pembro + CT, OS)

Figure 22. Parametric model hazard function plot (dMMR, Pembro + CT, OS)

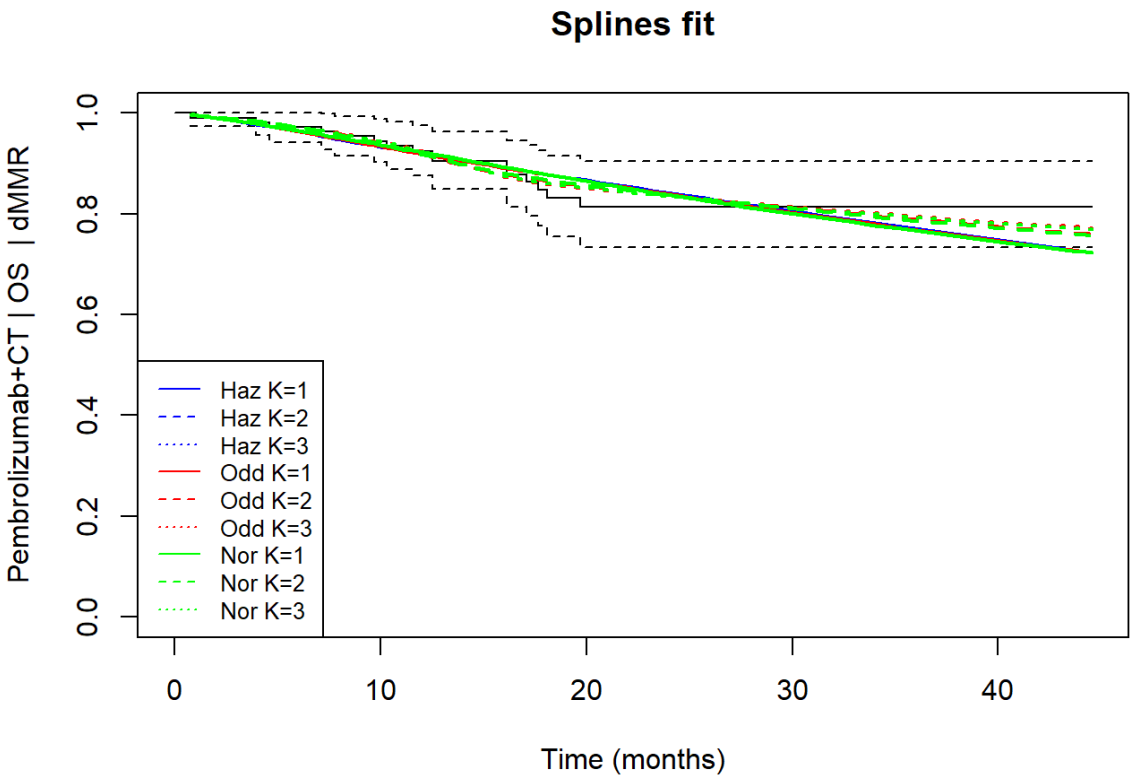

Figure 23. Spline model fit over trial length (dMMR, Pembro + CT, OS)

Figure 24. Spline model hazard function plot (dMMR, Pembro + CT, OS)

Table 24. Statistical model fit (dMMR, Pembro + CT, OS)

Model	AIC	BIC	AIC rank	BIC rank
Exponential	**192.1025**	**194.8029**	**Best**	**Best**
Weibull	193.9073	199.3083	Similar	Similar
Log-normal	193.0927	198.4937	Similar	Similar
Log-logistic	193.4752	198.8762	Similar	Similar
Gompertz	193.9482	199.3492	Similar	Similar
Generalised Gamma	195.0917	203.1931	Similar	
Gamma	193.8267	199.2277	Similar	Similar
Hazards k=1	195.7026	203.8041	Similar	
Hazards k=2	NA	NA		
Hazards k=3	NA	NA		
Odds k=1	195.3957	203.4971	Similar	
Odds k=2	195.8219	206.6238	Similar	
Odds k=3	197.4079	210.9103		
Normal k=1	194.8541	202.9556	Similar	
Normal k=2	195.6898	206.4917	Similar	
Normal k=3	197.2784	210.7808		

pMMR subgroup

CT only (PFS)

Figure 25. Parametric model fit over trial length (pMMR, CT only, PFS)

Figure 26. Parametric model fit over 20 years (pMMR, CT only, PFS)

Figure 27. Parametric model hazard functions plot (pMMR, CT only, PFS)

Figure 28. Spline model fit over trial length (pMMR, CT only, PFS)

Figure 29. Spline model hazard functions plot (pMMR, CT only, PFS)

Table 25. Statistical model fit (pMMR, CT only, PFS)

Model	AIC	BIC	AIC rank	BIC rank
Exponential	1378.161	1381.862		
Weibull	1342.617	1350.017		
Log-normal	1305.333	1312.733		Similar
Log-logistic	1306.984	1314.385		Similar
Gompertz	1374.319	1381.72		
Generalised Gamma	1303.633	1314.735		Similar
Gamma	1327.624	1335.024		
Hazards k=1	**1299.93**	**1311.031**	**Similar**	**Best**
Hazards k=2	**1298.355**	**1313.157**	**Best**	Similar
Hazards k=3	1300.067	1318.569	Similar	
Odds k=1	1300.364	1311.465	Similar	Similar
Odds k=2	1299.294	1314.096	Similar	Similar
Odds k=3	1299.905	1318.407	Similar	

Normal k=1	1304.031	1315.133		Similar
Normal k=2	1298.635	1313.437	Similar	Similar
Normal k=3	1298.81	1317.313	Similar	

CT only (OS)

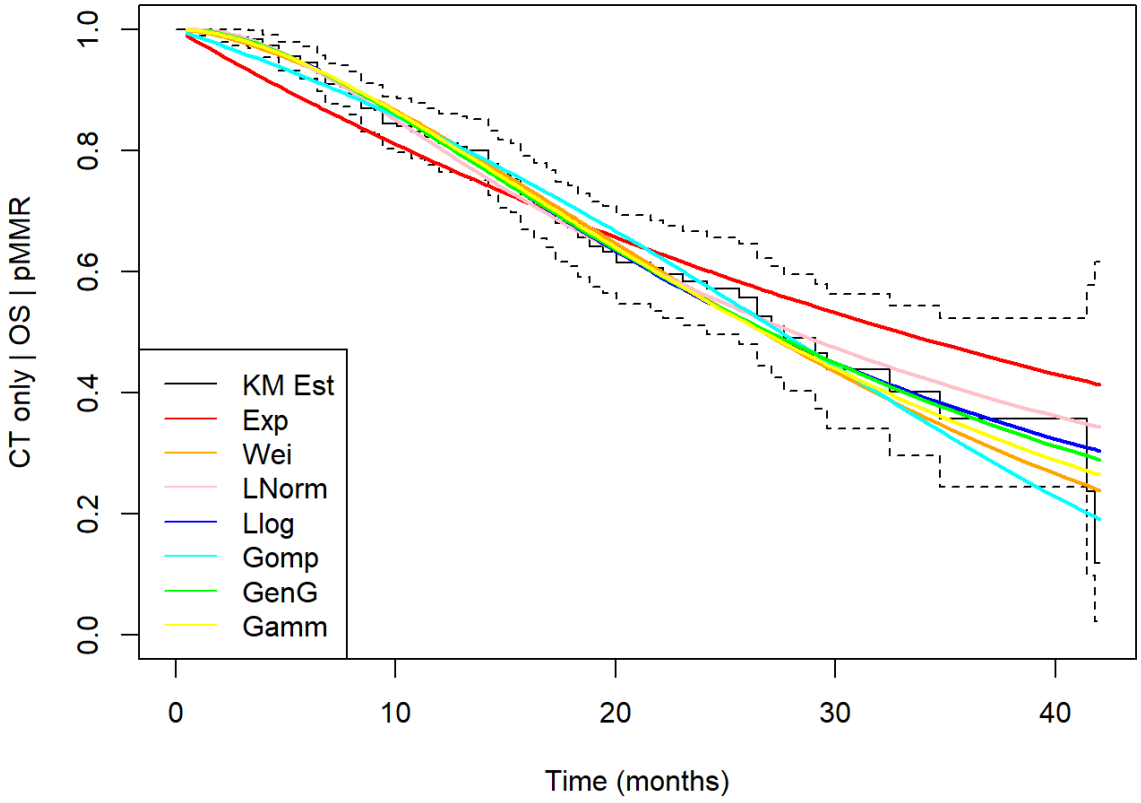

Figure 30. Parametric model fit over trial length (pMMR, CT only, OS)

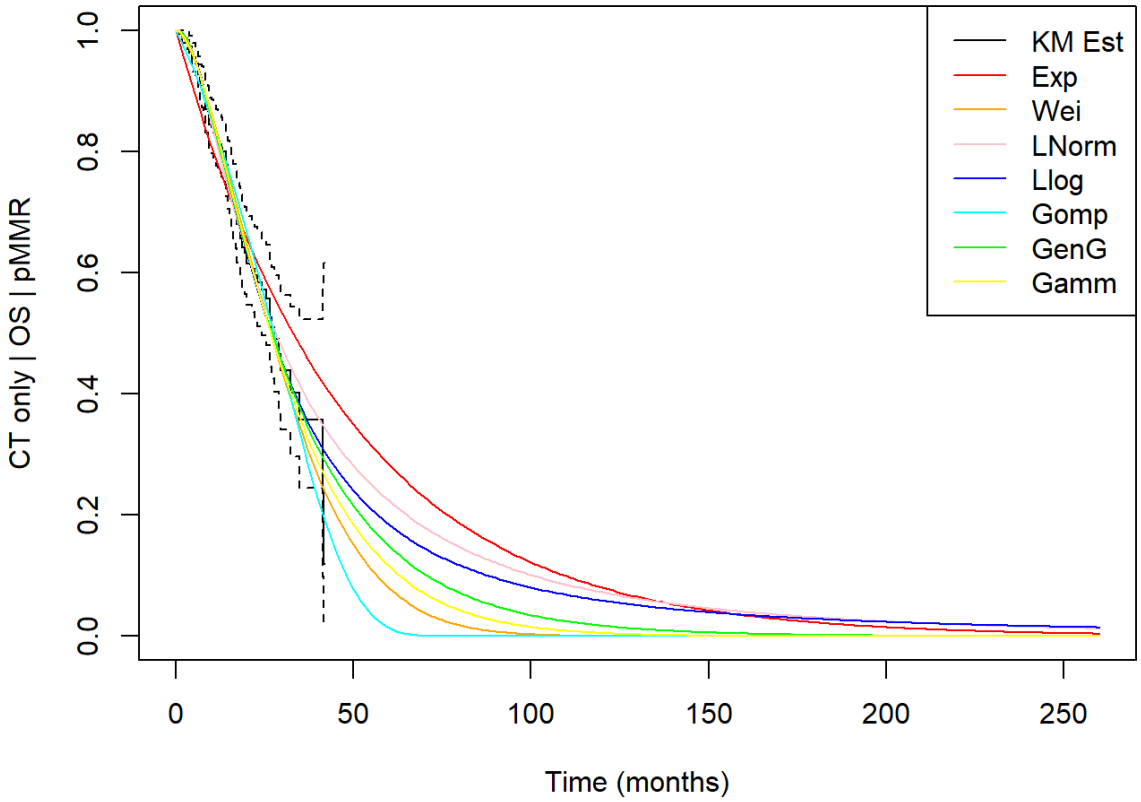

Figure 31. Parametric model fit over 20 years (pMMR, CT only, OS)

Figure 32. Parametric model hazard functions plot (pMMR, CT only, OS)

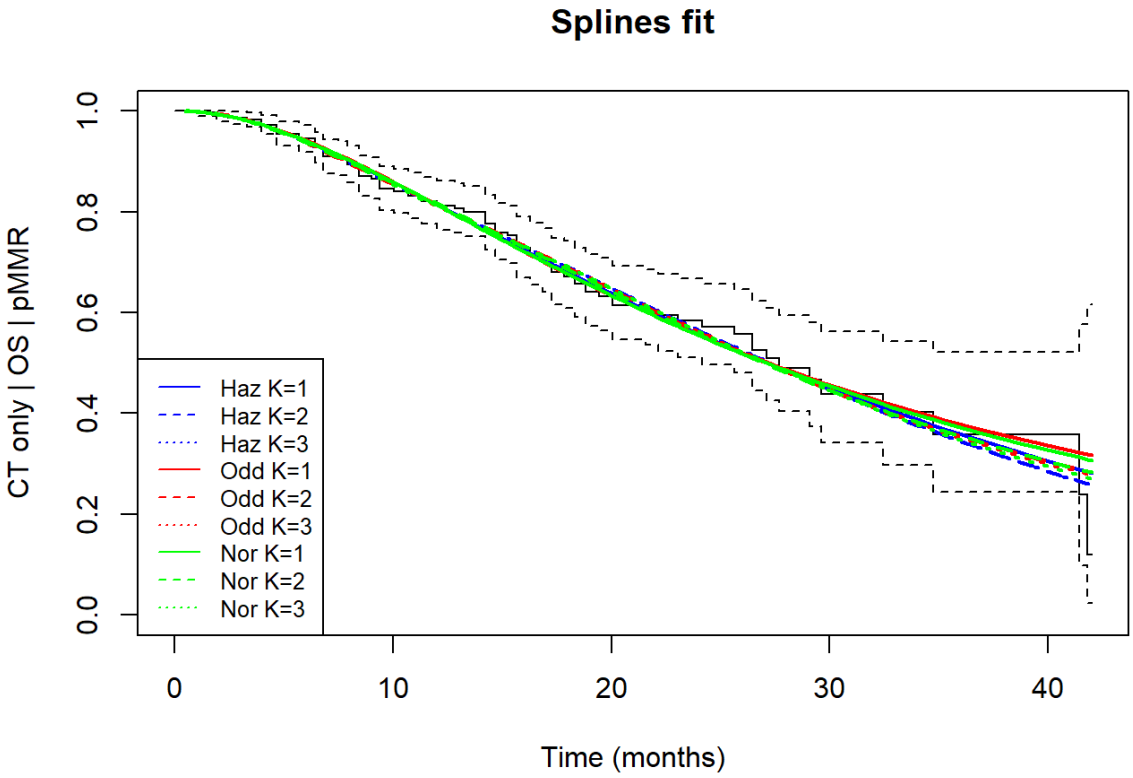

Figure 33. Spline model fit over trial length (pMMR, CT only, OS)

Figure 34. Spline model hazard functions plot (pMMR, CT only, OS)

Table 26. Statistical model fit (pMMR, CT only, OS)

Model	AIC	BIC	AIC rank	BIC rank
Exponential	906.5028	910.2032		
Weibull	882.6766	890.0775	Similar	Similar
Log-normal	883.0764	890.4773	Similar	Similar
Log-logistic	882.3308	889.7316	Similar	Similar
Gompertz	891.1591	898.56		
Generalised Gamma	883.2572	894.3586	Similar	
Gamma	**881.5766**	**888.9775**	**Best**	**Best**
Hazards k=1	882.8736	893.975	Similar	Similar
Hazards k=2	884.1672	898.9689	Similar	
Hazards k=3	886.3696	904.8718	Similar	
Odds k=1	884.1634	895.2647	Similar	
Odds k=2	884.8031	899.6049	Similar	
Odds k=3	886.9745	905.4767		

Normal k=1	883.6905	894.7919	Similar	
Normal k=2	885.1027	899.9045	Similar	
Normal k=3	886.7418	905.2441		

Pembrolizumab + CT (PFS)

Figure 35. Parametric model fit over trial length (pMMR, Pembro + CT, PFS)

Figure 36. Parametric model fit over 20 years (pMMR, Pembro + CT, PFS)

Figure 37. Parametric model hazard functions plot (pMMR, Pembro + CT, PFS)

Figure 38. Spline model fit over trial length (pMMR, Pembro + CT, PFS)

Figure 39. Spline model hazard functions plot (pMMR, Pembro + CT, PFS)

Table 27. Statistical model fit (pMMR, Pembro + CT, PFS)

Model	AIC	BIC	AIC rank	BIC rank
Exponential	1304.29	1307.987		
Weibull	1292.992	1300.386		
Log-normal	1268.061	1275.455		
Log-logistic	1268.868	1276.262		
Gompertz	1306.194	1313.589		
Generalised Gamma	1268.816	1279.907		
Gamma	1285.999	1293.393		
Hazards k=1	1263.741	1274.832		
Hazards k=2	**1248.968**	**1263.757**	**Best**	**Best**
Hazards k=3	1251.57	1270.056	Similar	
Odds k=1	1263.657	1274.748		
Odds k=2	1250.226	1265.014	Similar	Similar

Odds k=3	1251.84	1270.325	Similar	
Normal k=1	1269.282	1280.373		
Normal k=2	1250.884	1265.673	Similar	Similar
Normal k=3	1251.25	1269.735	Similar	

Pembrolizumab + CT (OS)

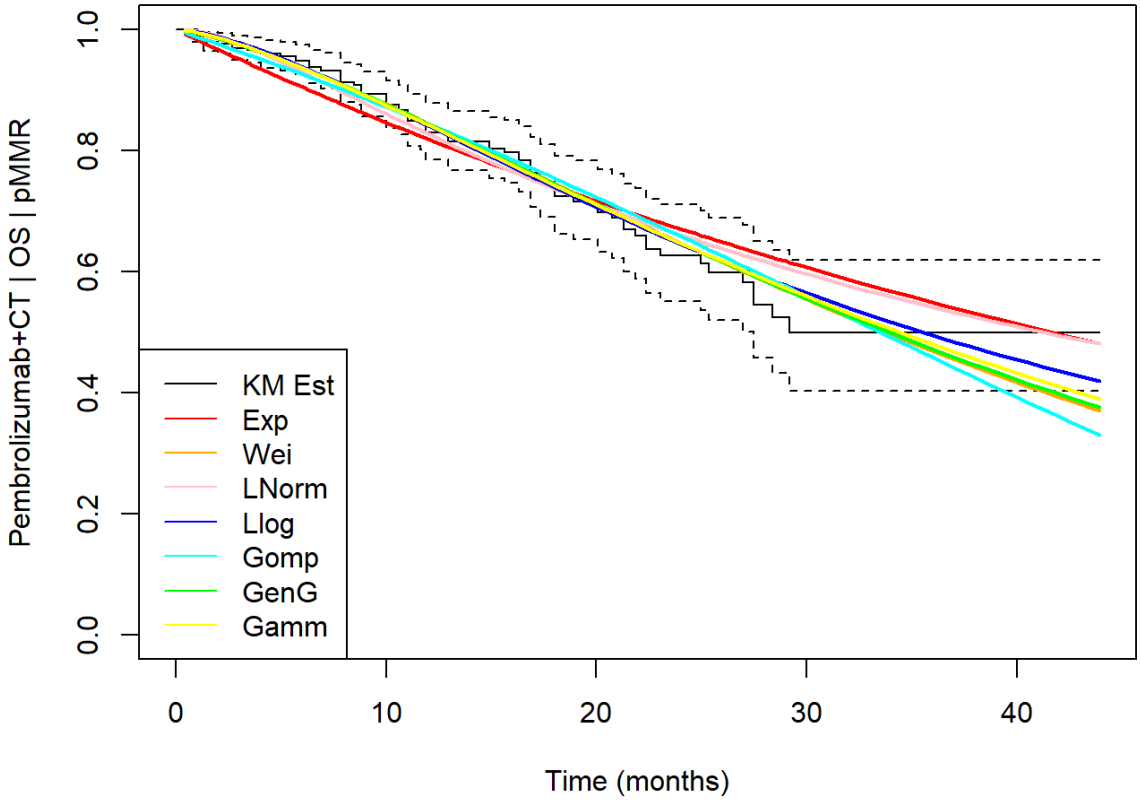

Figure 40. Parametric model fit over trial length (pMMR, Pembro + CT, OS)

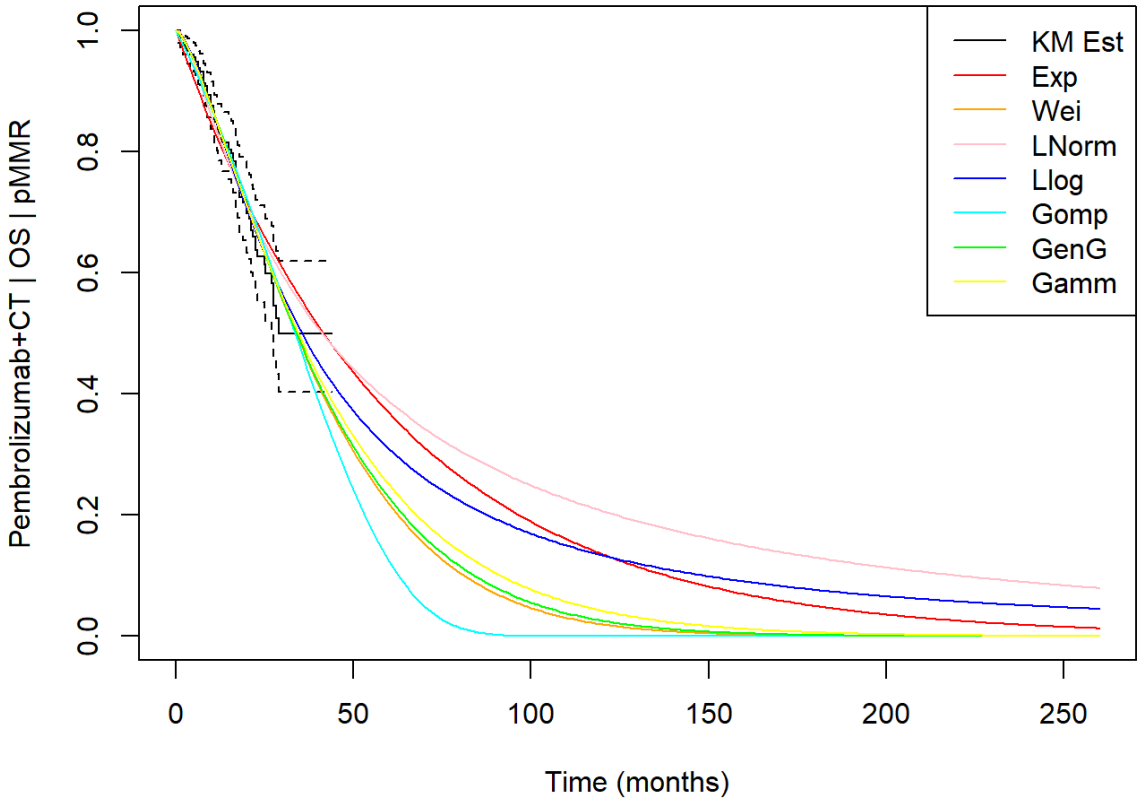

Figure 41. Parametric model fit over 20 years (pMMR, Pembro + CT, OS)

Figure 42. Parametric model hazard functions plot (pMMR, Pembro + CT, OS)

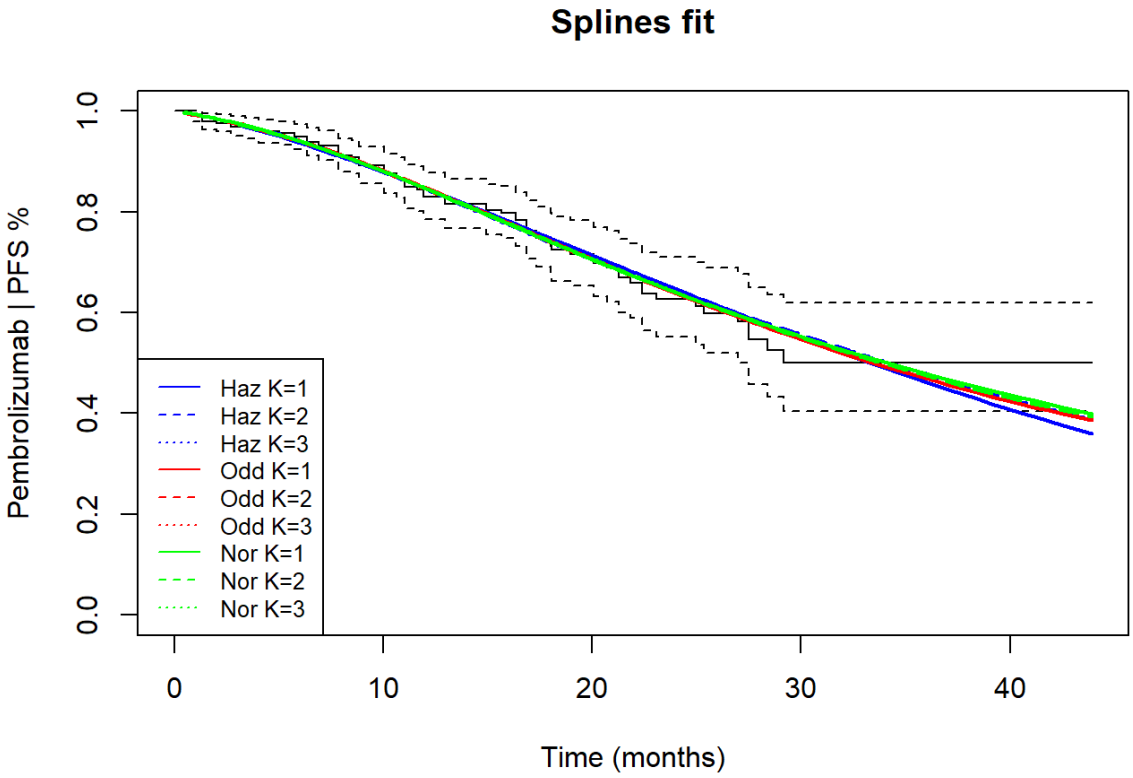

Figure 43. Spline model fit over trial length (pMMR, Pembro + CT, OS)

Figure 44. Spline model hazard functions plot (pMMR, Pembro + CT, OS)

Table 28. Statistical model fit (pMMR, Pembro + CT, OS)

Model	AIC	BIC	AIC rank	BIC rank
Exponential	786.8269	790.524		Similar
Weibull	779.5213	786.9155	Similar	Similar
Log-normal	785.1901	792.5843		
Log-logistic	779.5003	786.8945	**Best**	**Best**
Gompertz	782.8405	790.2347	Similar	Similar
Generalised Gamma	781.5019	792.5932	Similar	
Gamma	779.5904	786.9845	Similar	Similar
Hazards k=1	781.399	792.4903	Similar	
Hazards k=2	782.8147	797.603	Similar	
Hazards k=3	784.7755	803.261		
Odds k=1	780.2192	791.3104	Similar	Similar
Odds k=2	782.1489	796.9372	Similar	
Odds k=3	784.1311	802.6166	Similar	
Normal k=1	779.9208	791.0121	Similar	Similar
Normal k=2	781.8691	796.6575	Similar	
Normal k=3	783.8993	802.3848	Similar	

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Pembrolizumab with carboplatin and paclitaxel for untreated advanced or recurrent endometrial cancer

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Merck Sharp & Dohme (UK) Ltd

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Overview	
0	Thank you for the opportunity to comment on the Draft Guidance (DG) for this Technology Appraisal. MSD is pleased that the committee recognise the unmet need for effective, innovative treatment options for primary advanced or recurrent endometrial cancer and that pembrolizumab in combination with carboplatin + paclitaxel (CT) is effective at improving progression-free survival (PFS). MSD emphasises the comments from patient and clinical experts stated in the [final] draft guidance for two recent appraisals of other immunotherapies (NICE ID6426 and ID6317). That is,

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	that having to wait until progression to access immunotherapy means many patients (around one third) will not be fit enough to receive effective treatment; therefore bringing immunotherapy earlier in the pathway gives more patients the opportunity to benefit.[1,2] As noted in the DG, MSD's submission focused on the all comer population, to best reflect the marketing authorisation of pembrolizumab + CT, which indicates the treatment for patients independent of mismatch repair (MMR) status, and the NICE scope. In addition, this approach increases the size of the analysis population which in turn reduces uncertainty in the overall study results and long-term extrapolations. Therefore, MSD consider it appropriate to assess the decision problem in this larger pooled cohort. However, MSD also recognises that MMR status is an important predictor of response and survival outcomes with immunotherapy in this cancer. As such, subgroup analysis results for dMMR and pMMR cohorts from the trial and economic analysis were presented separately in the company submission and appendices, along with details of the methods and assumptions used in these subgroup analyses. Supplementary evidence relating to the economic analyses in these subgroups was subsequently provided upon request by NICE. MSD highlight that the KEYNOTE-868 (NRG-GY018) trial was designed to formally assess the efficacy of pembrolizumab + CT in each of the MMR subgroups, enabling more robust conclusions in these populations for the primary outcome (PFS), and in this regard it is unique amongst currently published trials of immunotherapy for primary advanced or recurrent endometrial cancer. MSD understands that the committee wishes to further consider the cost-effectiveness of pembrolizumab + CT in each MMR subgroup. Following the committee meeting, the EAG has reviewed the subgroup analyses previously submitted by MSD and has shared a report summarising their findings. In response to the DG we consider the EAG's findings, provide evidence that supports our modelling approach in these subgroups, and also address key uncertainties raised in the DG. The key topics addressed in MSD's response include: 1. Efficacy of pembrolizumab + CT in KEYNOTE-868 (NRG-GY018) (DG Section 3.4) 2. Modelling of MMR subgroups (DG Section 3.5) 3. Treatment effect waning (DG Section 3.10) 4. Subsequent treatment mix (DG Section 3.12) 5. Health state utility values (DG Section 3.9) 6. Resource use estimates (DG Section 3.11) 7. Starting age in the model (DG Section 3.8) In response to the DG, MSD presents an updated base case analysis for the dMMR and pMMR cohorts, incorporating the following changes based on the findings and evidence discussed: • Correction to resource use implementation to align with committee preferences • Updated baseline mean age to reflect NHS England data • Updated utility value for the progression-free health state, based on newly available data from KEYNOTE-B21 for patients with pMMR endometrial cancer • Updated subsequent treatment distributions to reflect clinical opinion from a wider range of experts in UK NHS practice and a recent NICE appraisal

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	The updated base case ICER is [redacted]/QALY for dMMR patients and [redacted]/QALY for pMMR patients. These ICERs, and all cost-effectiveness results in this document, assume list prices for any comparator treatments. A series of plausible scenarios for the dMMR and pMMR subgroups are also presented, with estimated ICERs that range between [redacted], for dMMR patients and [redacted] for pMMR patients. For completeness, the updated results for the all comer population are also presented. The economic results for the MMR subgroups are consistent with the conclusions in the all comer population, demonstrating that pembrolizumab + CT is cost-effective across the full licensed indication. Full details of MSD's updated base case and scenario analysis results across all three populations (dMMR, pMMR, and all comer) are provided in Appendix 1 at the end of this document.

1. Efficacy of pembrolizumab + CT in KEYNOTE-868 (NRG-GY018)

1	**Efficacy of pembrolizumab + CT in KEYNOTE-868 (NRG-GY018) (DG Section 3.4)** The DG states that whilst pembrolizumab + CT is significantly more effective at preventing progression or death than CT alone (i.e. it improves PFS), the improvement in overall survival (OS) is not statistically significant in either MMR cohort. KEYNOTE-868 (NRG-GY018) is the only published trial to date which has been designed to formally assess the efficacy of immunotherapy for primary advanced or recurrent endometrial cancer separately for dMMR and pMMR. A statistically significant improvement in the primary outcome (PFS) was observed for both MMR cohorts. MSD highlights that the trial was not powered to detect a statistically significant difference in OS between the treatment arms. However, Kaplan-Meier plots for both MMR cohorts show a clear separation between the OS curves indicating a positive trend for improved OS outcomes with pembrolizumab + CT versus CT alone. As such, the fact that OS was not statistically significant in the MMR subgroups in this trial should not be interpreted as evidence that pembrolizumab + CT does not improve OS. MSD also highlights that in the larger all comer cohort presented in the submission, whilst this also cannot be formally tested, the confidence intervals for the OS analysis do not cross one (HR [95% CI] 0.74 [0.57, 0.97]), indicating that pembrolizumab + CT did demonstrate an improvement in OS in the overall population.

2. Modelling of MMR subgroups

2	**Modelling of MMR subgroups (DG Section 3.5)** MSD understands that the committee wishes to further consider the cost-effectiveness of pembrolizumab + CT in each MMR subgroup. Further details on the process and rationale for selecting curves to model PFS and OS in each subgroup were provided to NICE following the committee meeting ("MMR Subgroups" supplement); MSD therefore request that this document is referred to if additional rationale are required. Following initial feedback from the EAG after the committee meeting on the subgroup analyses included in the company submission/appendices, and clinical expert opinion expressed at the committee meeting, MSD has reviewed the choice of models used to extrapolate the trial data in each MMR subgroup to ensure that the projected estimates are as robust as possible. ***dMMR***

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Taking into account the EAG's assessment of the company's dMMR modelling, MSD and the EAG are aligned on the overall survival (OS) estimates for both CT and pembrolizumab + CT arms. A scenario analysis using alternative selections (CT, gamma; Pembrolizumab + CT, log-normal) that align long-term OS more closely with committee-preferred OS estimates in NICE ID6426[1] is explored for completeness to help understand the impact of OS curve choice in the dMMR cohort (Appendix 1.1.3); pembrolizumab + CT remains highly cost-effective.

The company and EAG differ in their choice of PFS extrapolation models (Figure 1), although the choice of curves has minimal impact on the ICER ([redacted]):

- PFS: Pembrolizumab + CT arm
    - Both the company and EAG selections were highlighted as plausible by experts at the company advisory board.
    - Comments from the advisory board experts about expectations for an earlier and flatter plateau align with MSD's selection of the **generalised gamma** curve over the more pessimistic log-logistic curve (Section 1.1.1, MMR subgroup supplement). This is consistent with expert advice cited in NICE TA963.[3] MSD notes that the predicted long-term PFS predicted by the current model is more conservative than the preferred estimates for PFS with immunotherapy in NICE ID6426,[1] and also notes the EAG's comment about standard parametric models (which includes both the MSD- and EAG-preferred curves) being pessimistic.
- PFS: CT arm
    - The difference in long-term estimates between MSD's choice (two-piece gamma) and the EAG's choice (generalised gamma) is minimal. MSD's selection results in marginally higher PFS estimates in the short term (between 2-5 years), whereas the EAG choice predicts higher PFS in the longer term (5+ years).
    - As discussed in MSD's submission (CS Appendix O and MMR subgroups supplement), all standard parametric extrapolations produced a very poor fit to the trial PFS data. It is unclear from the EAG's response if they assessed the 2-piece curves that were provided in the submission, but no critique of the company's choice has been provided. The **2-piece gamma** remains MSD's preferred base case, given that had it an improved visual fit vs. standard extrapolations and was the preferred curve of experts participating in an advisory board.

While the EAG's selections for PFS were broadly in line with the company's, MSD retains the original submitted base case curves based on clinical expert input from the advisory board and improved visual fit.

Figure 1. Company and EAG PFS curve selections: dMMR

[redacted]

Key: CT, chemotherapy; P+CT, pembrolizumab + chemotherapy; PFS, progression free survival

pMMR

OS: Pembrolizumab + CT

- MSD selected the standard **log-logistic** model due to its good statistical fit, best overall visual fit to hazards, and concordance with clinician expectations at the advisory board (further details in CS Appendix O and MMR Subgroups supplement). Spline models did not provide an improved statistical or visual fit.

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- The log-logistic curve was also identified as a plausible curve by the EAG, although no specific critique or rationale was provided for the EAG to prefer the selection of the 1-knot normal (EAG base case) over the log-logistic.
- As highlighted by one of the clinical experts at the committee meeting (DG, section 3.2), and supported by the response rates in KEYNOTE-868 (complete response [CR] rate 14%), some pMMR patients are still expected to have a very good, long-term response to pembrolizumab + CT. This is better captured using the log-logistic (MSD's preferred curve) vs. the 1-knot normal (EAG's preferred curve).
- Therefore, MSD considers that the standard log-logistic extrapolation is the most appropriate pembrolizumab + CT pMMR OS curve for decision making, and that the 1-knot hazard is an overly pessimistic choice from the EAG.

<u>OS: CT arm</u>

- MSD selected the **gamma** curve for CT OS based on best statistical and visual fit and clinical input from an advisory board; experts felt that the gamma curve best represented the expected shape of the OS curve for the pMMR CT arm (further details provided in CS Appendix O and MMR Subgroups supplement). As with the pembrolizumab + CT OS selections, the EAG identified MSD's gamma curve to be a plausible selection but did not provide an in-depth rationale for preferring the 1-knot hazard (EAG base case) over the gamma.
- Both MSD's and the EAG's CT OS selections result in similar extrapolations, with long-term estimates deviating by approximately 1% at 2, 5, 10 and 20 years.
- Given the alignment from the advisory board and the EAG's identification of it as a plausible curve, MSD considers the gamma distribution to be the most appropriate curve to model OS outcomes in for the CT arm.
    - Based on additional comments made by experts at the advisory board that the real-world tail of the gamma curve could potentially be higher than that shown to them in the meeting, and the fact that some pMMR patients may still see a durable response to IO that they may then receive in the second-line setting, MSD have also presented a scenario that explores a curve similar to gamma, but with a flatter tail, the **2-knot odds** (Figure 15). This also had a good statistical fit and representation of the hazard profile (CS Appendix O and MMR Subgroups supplement).

<u>PFS</u>

The EAG's selections for both pembrolizumab + CT and CT lack face validity. The implied PFS HR rises above 1 after just 2 years, resulting in the CT PFS curve being higher than the pembrolizumab + CT PFS curve after 5.5 years – given the observed treatment effect (PFS HR [redacted]) and overall response rates in the KEYNOTE-868 (NRG-GY018 trial), this is not clinically plausible. The complete response rate in the pembrolizumab arm was 6% higher than in the CT arm, with partial response being 7% higher, and therefore crossing PFS curves at 5 years is implausible

- *<u>CT arm</u>*:
    - MSD's preferred curve was the **1-knot odds spline**, selected based on its excellent visual fit and concordance with clinical experts' predictions.
    - Landmark estimates from MSD's advisory board also suggested that PFS rates at 5 years would be 2-3% for the CT arm but the EAG's CT arm (2-knot hazard)

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	estimates >10% PFS rates at 5 years, suggesting the EAG's curve is overly optimistic. • *Pembrolizumab + CT arm*: ○ The EAG highlight that the 2-knot splines provided the best visual fit but then selected the 1-knot hazard, that has poor visual fit to the observed data, especially in the tail. MSD's selection of the **2-piece log-logistic** sits in a middle ground between the 1-knot and 2-knot splines. ○ MSD also provided a scenario analysis using 2-knot normal due to its good statistical and visual fit to the tail (MMR Subgroups supplement). This curve was also considered plausible by the EAG. Therefore, MSD considers that retaining the Company base case is the most appropriate pMMR PFS curve selection for decision making.

3. Treatment effect waning (TEW)

3	**Treatment effect waning (DG section 3.10)** In the DG, the committee requested rationale to explain why the impact of applying treatment effect waning (TEW) on QALY gains was smaller than expected and a scenario, by MMR status, where TEW applies to all patients regardless of response status. Both requests will be addressed in this response. However, based on the available evidence, MSD disagrees that TEW should be applied; additional justification for this is therefore also provided. This response is structured as follows: 1. Justification for not applying TEW 2. Scenarios exploring impact of TEW ***1. Justification for not applying TEW*** Justification for not applying TEW falls under five key points: a) The mechanism of action of pembrolizumab supports a sustained treatment effect b) Longer term data from trials of immunotherapy treatments have shown a continued treatment effect post-discontinuation of treatment c) Observed data from the trial support a sustained treatment effect d) Certain survival models may already predict some degree of TEW e) Precedent in previous appraisals of treatments for endometrial cancer These points are discussed in turn in the following sections. a) The mechanism of action of pembrolizumab supports a sustained treatment effect.

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As immunotherapies act on the patient's immune system rather than directly on the tumour, the immune system will continue to recognise the cancer cells after treatment is stopped, which leads to durable responses and prolonged survival in some patients. Some key studies include:

- The Postow et al. 2015 review discusses how immune checkpoint inhibitors like anti-PD-1 and anti-CTLA-4 effectively unleash the immune system's ability to recognise and destroy tumour cells. The authors emphasise that these therapies can lead to long-lasting immune responses, which can persist even after treatment has ended.[4]
- In the Brahmer et al. 2010 trial, the researchers found that patients receiving treatment with an anti-PD-L1 antibody demonstrated durable responses, with the immune system continuing to target cancer cells after treatment cessation. This work helped to establish the long-term impacts of immunotherapies.[5]

Response data from KEYNOTE-868 (NRG-GY018) support this, demonstrating that treatment with pembrolizumab + CT is more likely to result in a response, and that the responses are more durable, than treatment with CT alone:

- The objective response (OR) rate was significantly higher in the pembrolizumab + CT arm compared with CT alone for both pMMR and dMMR cohorts (pMMR: 72.3% vs 59.0%, respectively; dMMR: 82.1% vs 71.6%, respectively). In addition, more patients achieved a complete response (CR) with pembrolizumab + CT arm compared with CT alone (pMMR: 14.3% vs 8.4%; dMMR: 31.6% vs 13.7%).
- The median duration of response (DOR) amongst responders was longer in pembrolizumab-treated patients than patients who received CT alone, with the DOR Kaplan-Meier curves for both MMR cohorts plateauing at 1-2 years (CS Appendix Figure 8−9). This indicates that amongst responders, the risk of progression or death is lower and more durable for the pembrolizumab + CT arm vs CT alone, and it decreases over time.

Additionally, clinical experts consulted as part of two recent NICE appraisals for other immunotherapies for first-line endometrial cancer "*said that if there is a sustained response to treatment after 3 years then it would be assumed that further progression events or death do not occur past this timepoint*" (ID6317).[2] At the committee meeting for NICE ID6426, experts explained that immunotherapy therapy studies in different tumour types typically show a sustained benefit after stopping treatment, particularly among patients who have a CR.[1]

b) <u>Longer-term data from trials of immunotherapy treatments have shown a continued treatment effect post-discontinuation of treatment.</u>

Despite the extensive precedent in the application of treatment waning hypothetically, there remains no concrete and substantial evidence of treatment waning effect for immunotherapies, which includes pembrolizumab. The CDF clinical lead has previously explained in NICE appraisals of immunotherapies (e.g. TA1030) that, "…*in many trials of immunotherapies for metastatic NSCLC (which are now quite mature) there was no substantial evidence of treatment-effect waning, and agreed with the company that if waning of treatment effect were to occur it would likely be visible in the company's data. The clinical expert also thought that there was not likely to be a waning of treatment effect beyond the observed data.*"[6]

- In KEYNOTE-158, which investigated up to 2 years of pembrolizumab monotherapy for patients with previously treated dMMR tumours and had 6 years of Kaplan-Meier data, 70.1% of responders across tumour types were still in response at 3 years with DOR

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Kaplan-Meier data demonstrating a clear plateau from approximately 2 years.[7] At the latest database lock ([redacted]), amongst the 42 patients with a response in the subgroup of patients with endometrial cancer (n=83), [redacted] were still in response at 3, 4 and 5 years. This indicates that patients, including those with dMMR endometrial cancer, have a highly durable response to treatment with immunotherapy even following discontinuation of therapy.

- KEYNOTE-006 represents the longest follow-up (median 10 years) from a phase 3 trial of anti-PD-1/L1 therapy (up to 2 years of pembrolizumab, for advanced melanoma) available to date. There was no narrowing of the OS Kaplan-Meier curves or treatment effect over this extended follow-up (OS HR was 0.73, 0.7 and 0.71 at 5, 7 and 10 years, respectively).[8-10] OS was markedly improved in patients who had a response to pembrolizumab compared with non-responders (8-year OS 78.1%, 58.7% and 21.8% for CR, PR and non-responders, respectively), and this trend was still observed at 10 years.[8] In addition, the long-term outcomes observed in KEYNOTE-006 with patients treated up to 2 years are generally consistent with those observed in the melanoma cohort of KEYNOTE-001, which did not include a 2-year stopping rule.
- In KEYNOTE-024 (a trial of pembrolizumab monotherapy in PD-L1 ≥50% NSCLC), there was no narrowing of the PFS or OS treatment benefit of pembrolizumab monotherapy versus chemotherapy through 5 years of follow-up (OS HR at 11.2 months was similar to the HR at 5 years, with a sustained separation of the curves), despite a high degree of crossover to pembrolizumab among those who progressed on chemotherapy.[11-13]

c) Observed data from the trial support a sustained treatment effect

Based on the KEYNOTE-868 (NRG-GY018) trial data for pembrolizumab + CT and CT, there is no clear evidence to indicate TEW as the Kaplan-Meier curves for PFS and OS separated early and remained separated throughout the evaluation period in favour of pembrolizumab + CT (CS Appendix Figures 4−7). Also, the HR over the trial period suggests that the long-term benefits of pembrolizumab are stable or continuing to diverge after approximately 100 weeks of treatment, in the dMMR and pMMR cohorts as well as in the all comer population (Figure 2).

Figure 2. Observed time-dependent OS HR in KEYNOTE-868 (NRG-GY018)

[redacted]

Abbreviations: HR, hazard ratio; OS, overall survival.
(A) dMMR cohort; (B) pMMR cohort; (C) All comer population. Note that the divergence of the confidence intervals in the latter stages is due to small number of remaining patients at risk.

d) Certain survival models may already predict some degree of TEW

Application of TEW is a crude approach to explore the impact of loss of treatment effect over time and is highly dependent on the implied hazards in the comparator arm. However, as explained by Taylor et al, if the analysis uses independently fitted models which result in hazards that are converging over time, then it has already implicitly been assumed that the treatment effect wanes over time, without any TEW explicitly being applied.[14] This is often the case when the hazards in the comparator arm are assumed to decrease over time, for example to reflect the presence of long-term survivors. This is more plausible than artificially increasing the hazards in the intervention arm after a specified timepoint.

This trend is not observed in the base case analyses for dMMR and pMMR, which were selected based on clinical expert preferences from MSD's advisory board. Therefore, to explore

this approach to TEW, scenarios using alternative curves to model CT arm OS (selected based on good visual and statistical fit) are presented which estimate more optimistic long-term survival outcomes for the CT arm OS resulting in a flatter tail (dMMR, log-logistic; pMMR, 2-knot odds; see Appendix 2.1.2 and 2.2.2 for resulting OS curves). In each cohort, this represents a continuing reduction in the long-term CT arm hazards over time, which could reflect additional comments made by clinical experts at the advisory board that the tails in real-world practice could be slightly higher than those presented to them, and also capture the potential impact of subsequent immunotherapy that certain CT patients receive. In these scenarios, the hazards are already notably converging and therefore TEW is already predicted by the models (Figure 3). Additional application of waning would represent double counting of this effect.

Figure 3. Modelled OS hazards for OS in key scenario analyses

[redacted]

Abbreviations: HR, hazard ratio; OS, overall survival.
(A) Modelled hazards for OS, dMMR scenario (CT arm: log-logistic); (B) Modelled hazards for OS, pMMR scenario (CT arm: 2-knot odds).

Additionally, an analysis from 2023 explored the predictive accuracy of a range of TEW methods when applied to extrapolations based on early data cuts for pembrolizumab across six NICE oncology appraisals, and then compared the output against observed data from longer follow-up. The authors concluded that "*For OS extrapolations based on clinical plausibility as well as goodness-of-fit, applying treatment waning resulted in pessimistic predictions, with almost all predicted LYs being lower than realised LYs*."[15] As the extrapolations applied in the current economic analysis for dMMR and pMMR (base case and scenario analyses) were selected based on both clinical plausibility (with input from clinical experts) and statistical fit, application of TEW may result in underestimation of the long-term treatment benefit of pembrolizumab.

e) <u>Precedent in previous appraisals of treatments for endometrial cancer</u>

Based on the clinical evidence, and NICE precedent, for immunotherapies (including pembrolizumab) in endometrial cancer, application of TEW would be considered highly conservative:

- In the recent DG for NICE ID6317, and final draft guidance for NICE ID6426, for other immunotherapies in first-line dMMR endometrial cancer, the committee's assumptions did not include applying TEW despite applying a treatment cap at 3 years.[1,2]
- In the final draft guidance for NICE TA914 (based on KEYNOTE-158; pembrolizumab for previously treated dMMR/MSI-H tumours, including endometrial cancer) it states "*…the committee concluded that the applying treatment waning from 7 to 9 years was a reasonable and potentially conservative assumption based on the data provided for this particular indication*."[16]
    - Clinical opinion cited in TA914 suggests a 'functionally cured' group of patients at 5 years, which would be contradicted by applying TEW.
    - This was a second-line indication; response rate data (Table 3) and clinical opinion support that response rates to immunotherapy are higher when used first-line, therefore this TEW assumption should be considered even more conservative if applied in the first-line setting.[1]

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	2. Scenarios exploring TEW
	For the reasons outlined above, no TEW is assumed in the base case analysis. In TEW scenario analyses previously explored by MSD and the EAG, waning was assumed to apply only to patients who did not have an OR (24.8% of the all comer population), therefore the impact of TEW was small. However, to acknowledge uncertainty surrounding a sustained treatment effect, and in response to the committee's request in the DG, additional conservative scenarios aligned with those in two recent NICE appraisals of pembrolizumab (TA997 and TA914) are considered.[16,17]
	To reflect (a) TA997 committee opinion that "*scenarios in which waning starts at either 5 years, 6 years or 7 years after starting treatment and reduce to the same as the comparator after 2 years, were all plausible*" and TA914 committee opinion that "*applying treatment waning from 7 to 9 years was a reasonable and potentially conservative assumption [in dMMR indications]";* and (b) clinical opinion from TA997 that "*for the [proportion] of people whose cancer has a complete response, treatment-effect waning would not be expected*",[17] the following scenarios were explored:
	• Gradual TEW applied at a starting timepoint of 7 years after the start of pembrolizumab + CT treatment, with the cycle-specific hazard for pembrolizumab + CT equalling the CT arm 2 years later (9 years).
	• Two assumptions were explored whereby TEW is applied to a specified proportion of patients:
	  ○ No-CR: The proportion of patients who did not have a CR (pMMR: 85.7%; dMMR: 68.4%)
	  ○ All: 100% of patients
	Applied to MSD's updated base case, TEW resulted in:
	• dMMR ICERs:
	  ○ No-CR patients, [redacted]/QALY (no-CR patients, 7-9 years)
	  ○ All patients, [redacted]/QALY (all patients, 7-9 years)
	• pMMR ICERs
	  ○ No-CR patients, [redacted]/QALY (no-CR patients, 7-9 years)
	  ○ All patients, [redacted]/QALY (all patients, 7-9 years)
	Given the rationale provided above, MSD do not consider this application of TEW to be appropriate. However, if such TEW is to be considered then MSD consider the scenarios applying waning to the proportion of patients who did not have a CR to be the most informative and clinically appropriate. Alternative scenarios provided by MSD, which estimate a flatter tail in the CT arm, already predict a degree of TEW and may be a more plausible representation of how hazards change over time than the artificial application of TEW.

4. Subsequent treatment mix

4	**Subsequent treatment mix (DG Section 3.12)** In the DG, the committee requests further analysis of the assumptions regarding the subsequent treatment mix used in the model. MSD has therefore:

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	1. Sought further evidence to inform the subsequent treatment assumptions in UK practice; 2. Reviewed the subsequent treatment mix used in the trial and model, and; 3. Considered important implications regarding the subsequent mix applied in the model. ***1. <u>Evidence of subsequent treatment mix in UK clinical practice</u>*** MSD sought further evidence to inform the subsequent treatment assumptions; specifically, **the proportion of patients who receive immunotherapy (IO) after progression in the CT arm**, which is a key model driver. • MSD contacted NHS England, via NICE, to request details relating to the number of patients in each MMR cohort who progressed on or following first-line carboplatin + paclitaxel in 2024, and the number of patients who received second-line IO in 2024 following progression on or after carboplatin + paclitaxel. However, no data were received in response to this request. • MSD sought input from 11 clinical experts from across the UK to further understand the real-world treatment patterns relating to the use of IO as second-line treatment after progression on or following treatment with carboplatin + paclitaxel (full details in Appendix 4). The findings from this exercise are summarised here **(see full details in Table 20, Appendix 4)**: • <u>dMMR</u> The experts stated that most patients (average estimate: 80-84%) with dMMR tumours who get active second-line treatment would get IO. This was aligned with the experts at the committee meeting, who also explained that "*Because of lenvatinib's toxicity, most people with dMMR endometrial cancer would have pembrolizumab monotherapy*". **Applying this to the proportion of patients who get *any* second-line treatment, on average they estimated that 62−66% (64−69% excluding outlier) of all dMMR patients who progressed on first-line CT would get IO.** • <u>pMMR</u> Aligned with the clinical experts at the committee meeting, and those consulted by the EAG, who "*explained that almost everyone with pMMR cancer who had chemotherapy as first-line treatment started pembrolizumab with lenvatinib at second line*", the experts consulted by MSD stated that pembrolizumab + lenvatinib would be the preferred treatment option after first-line CT for patients who were fit enough (IO monotherapy is not available for patients with pMMR tumours). On average, they estimated that 62−66% (67−71% excluding outlier) of patients who get active second-line treatment would get pembrolizumab + lenvatinib. **Applying this to the proportion of patients who get *any* second-line treatment, on average they estimated that 47−51% (50−55% excluding outlier) of all pMMR patients who progressed on first-line CT would get IO.** In addition, as explained by the CDF clinical lead at the committee meeting, patients who received IO at first-line would not be eligible to receive IO (i.e. pembrolizumab monotherapy or pembrolizumab + lenvatinib) at second-line. Note that the non-IO treatments (i.e. chemotherapy, hormone therapy and radiotherapy) used in practice and captured in the model are inexpensive and therefore the relative mix of these does not have a meaningful impact on the economic model results.

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2. Subsequent treatment mix used in model

MSD has reviewed the subsequent treatment assumptions used in the model in light of the additional evidence collected from clinical experts during and after the committee meeting. Data on first subsequent treatment use observed in the KEYNOTE-868 (NRG-GY018) trial amongst patients who progressed are presented in Table 17 and Table 18 of the Appendix of this document for dMMR and pMMR cohorts, respectively. A few specific adjustments were made to generate sets of market shares that reflect the available subsequent treatment options in the UK:

- For the pembrolizumab + CT arm, in both MMR cohorts IO use was set to zero, in line with clinical expert advice above, and shares for other treatments were proportionally adjusted
- For the CT arm:
  - dMMR: No further adjustments were made ([redacted] **of all patients who progress get second-line IO)**
  - pMMR: As pembrolizumab monotherapy is not available for pMMR disease, three alternative sets of market shares were generated to explore different methods of adjusting for this:
    a) pembrolizumab monotherapy market share is added to pembrolizumab + lenvatinib (i.e. it is assumed that patients who received IO monotherapy in the trial would get IO combination therapy if monotherapy was unavailable) **([redacted] of all patients who progress get second-line pembrolizumab + lenvatinib)**
    b) pembrolizumab monotherapy market share is proportionally redistributed across all other second-line therapies **([redacted] of all patients who progress get second-line pembrolizumab + lenvatinib)**
    c) pembrolizumab monotherapy market share is proportionally redistributed across all other 2L non-IO treatments **([redacted] of all patients who progress get second-line pembrolizumab + lenvatinib)**

The concordance of each set of market shares with the clinical expert opinion described above, in terms of subsequent IO use amongst patients who progress in the CT arm, was then assessed:

- dMMR: The advice received from clinical experts (62−69%) was closely aligned with the proportion of IO use in the trial ([redacted])
- pMMR: The average proportion of IO use estimated by the clinical experts (47−55%) aligned most closely with market share set (b) from the trial ([redacted]
  - MSD note that this is also aligned with the proportion of progressed patients receiving subsequent IO in the CT arm of the pMMR cohort in RUBY (68/133 = 51.1%).[18] RUBY data for dMMR were preferred by the committee in NICE ID6426 as most representative of NHS practice.[1]

In the original company submission, the subsequent treatment mix from the trial was modified based on specified proportions estimated by clinicians at MSD's advisory board, which suggested

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that only 40% of treated pMMR patients, and 80% of dMMR patients, would get subsequent immunotherapy. **However, having now gathered insights from a much wider range of clinical experts and additional sources as described above, MSD considers it necessary to amend the subsequent treatment mix applied in the model to better reflect UK clinical practice and use observed in the trial**.

The trial data are used as described above; for pMMR, market share set (b) are used for the base case as these had closest alignment with clinical advice and NICE committee preferences in ID6426. The updated subsequent treatment mix applied in the updated base case model for dMMR and pMMR is presented in Table 1. The alternative treatment mix sets are explored in scenario analyses.

Table 1. Subsequent treatment mix applied in updated base case model

	dMMR		pMMR	
	Pembrolizumab + CT	**CT**	**Pembrolizumab + CT**	**CT (set [b])**
Carboplatin	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin + paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
Dostarlimab	[redacted]	[redacted]	[redacted]	[redacted]
Doxorubicin	[redacted]	[redacted]	[redacted]	[redacted]
Letrozole	[redacted]	[redacted]	[redacted]	[redacted]
Megestrol	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + lenvatinib	[redacted]	[redacted]	[redacted]	[redacted]
Radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]
No active treatment	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CT, carboplatin + paclitaxel.
Refers to set (b) in the subsequent treatment mix scenarios presented in Table 18.

3. Implications of subsequent treatment mix in model

In KEYNOTE-868 (NRG-GY018), a large proportion of all patients (>40%) in the CT arm received IO at any subsequent line and a relatively smaller proportion in the pembrolizumab + CT arm were rechallenged with IO at a subsequent line:

- dMMR: CT, 54/112 (48%) all patients; Pembrolizumab + CT, 11/110 (10%) all patients
- pMMR: CT, 122/299 (41%) all patients; Pembrolizumab + CT, 50/298 (17%) all patients.

As such, the OS data used to model outcomes will include the effect of this subsequent IO:

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- The trial data show that most progression events occur within the first year of treatment, so most patients who progress would already have started subsequent therapy within the trial follow-up – therefore the effect of subsequent treatment will already be captured in the trial OS data
- Eskander et al, 2025 present sensitivity analyses in the pMMR cohort which adjust for the effect of subsequent IO ± lenvatinib on OS in both trial arms (Table 2 and Figure 4),[19] based on the simplified two-stage approach developed by Latimer et al, 2014.[20] These analyses:
  - **Confirm that the effect of subsequent IO is already captured in the trial**
  - **In the CT arm: Demonstrate that subsequent IO has a meaningful impact on OS.** After adjustments, the Kaplan-Meier curve sits lower, the median OS decreases by 4 months, and the HR reduces from 0.8 to 0.7.
  - **In the pembrolizumab + CT arm: Demonstrate that the small amount of rechallenge with IO does not influence the OS results.** After adjustments, there is no discernible change to the Kaplan-Meier curve and the median OS is unchanged.

(Note: It was not feasible to conduct the sensitivity analysis for the dMMR cohort due to the small sample size which made the results highly uncertain. The sensitivity analysis results for the all comer cohort are therefore included in Table 2 and Figure 4 as this will capture the impact of subsequent IO in the dMMR cohort.)

Consequently, removing the subsequent IO rechallenge from the treatment mix in the pembrolizumab + CT arm to reflect UK practice is appropriate and is very unlikely to bias the results. However, because some progressed patients in the trial received IO at second subsequent line or later but the model treatment mix is based on first subsequent line and has been adjusted to represent UK clinical practice, all scenarios in the cost-effectiveness analysis assume a lower proportion of subsequent IO use amongst progressed patients in the CT arm than was observed in the KEYNOTE-868 (NRG-GY018) trial. Therefore, the results are likely to bias the ICER against pembrolizumab + CT to some degree by incorporating some additional efficacy but excluding the costs.

Table 2. OS results before and after adjustments to remove the effect of subsequent IO ± lenvatinib

OS	Before adjustment		After adjustment	
	Median OS (95% CI)	HR (95% CI)	Median OS (95% CI)	HR (95% CI)
pMMR				
Pembrolizumab + CT	28.9 (26.8−NR)	0.8 (0.89−1.08)	28.9 (24.9−NR)	0.70 (0.50−0.98)
Placebo + CT	28.7 (24.0−34.6)	-	24.8 (19.3−NR)	-
All comers				
Pembrolizumab + CT	[redacted]	[redacted]	[redacted]	[redacted]
Placebo + CT	[redacted]	-	[redacted]	-

Abbreviations: CI, confidence interval; HR, hazard ratio; NR, not reached; OS, overall survival.
Based on sensitivity analyses reported by Eskander et al, 2025.[19]

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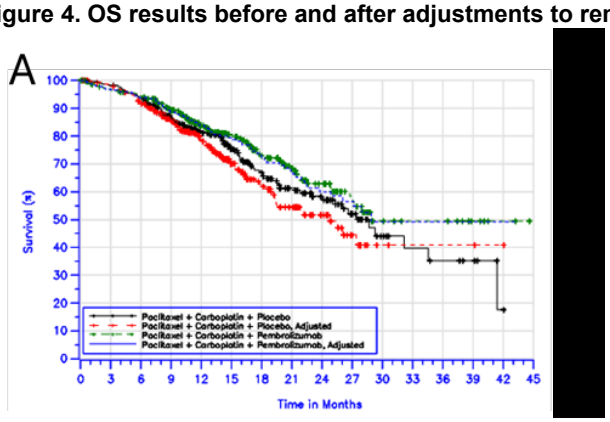
	Figure 4. OS results before and after adjustments to remove the effect of subsequent IO ± lenvatinib  (A) pMMR cohort; (B) All comer cohort. Based on sensitivity analyses reported by Eskander et al, 2025.[19]

5. Health state utility values

5	**Health state utilities values used in the model (DG Section 3.9)** In the DG, the committee states that the utility values used by MSD were appropriate to model the dMMR subgroup. However, the committee was uncertain whether these utility values, collected in dMMR patients, would be representative of the health-related quality of life (HRQoL) for patients with pMMR disease and requested the company to explore available sources of utility values by MMR subgroup or justify why the dMMR utilities from KEYNOTE-868 (NRG-GY018) are suitable for the pMMR subgroup. This response summarises evidence demonstrating that it is appropriate to assume the same utility values for dMMR and pMMR subgroups. It also presents newly available utility data for patients with pMMR tumours and provides updated cost-effectiveness results incorporating this evidence. ***Justification for using KEYNOTE-158 dMMR utilities for pMMR subgroup*** At the committee meeting, clinical experts explained that the key factors affecting HRQoL are (1) progression status and (2) treatment response. As stated by a clinical expert in NICE TA904, dMMR patients are '*generally (but not always) considered to have a better treatment response and prognosis than pMMR tumours, and most importantly are more likely to respond to immunotherapy*',[21] and, as observed in KEYNOTE-868 (NRG-GY018), have improved PFS (i.e. progression) outcomes compared with pMMR patients. The relevance of these observations to the economic analysis are therefore considered: 1. The impact of MMR status on progression and HRQoL The impact of progression on HRQoL is widely acknowledged and therefore incorporated into the design of most oncology models as standard. The impact of MMR status on progression is therefore already accounted for in the model, as health states are inherently defined by progression status and different utility values are applied to each model health state. As such, any differences in HRQoL based on progression status are already captured in the model. 2. Impact of MMR status on treatment response and HRQoL *a. Higher response rates in KEYNOTE-868 pMMR than KEYNOTE-158 dMMR*

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Firstly, comparison of treatment response rates for dMMR patients treated with pembrolizumab in the endometrial cancer cohort of KEYNOTE-158 with pMMR patients treated with pembrolizumab + CT in KEYNOTE-868 shows that complete response (CR) rates are highly comparable (14.3% KEYNOTE-158 dMMR vs. 15.7% KEYNOTE-868 pMMR), but partial response (PR) (and therefore objective response [OR]) rates are in fact higher in KEYNOTE-868 pMMR patients (PR: 58.0%; OR: 72.3%) than KEYNOTE-158 dMMR patients (PR: 34.9%; OR: 50.6%) (Table 3).

This is likely due to KEYNOTE-158 being conducted in the second-line (and later) setting vs. KEYNOTE-868 in the first-line setting, indicating that response rates to immunotherapy (in combination with CT) are higher when it is used first-line, regardless of MMR status. **This suggests that the dMMR utilities from KEYNOTE-158 may in fact be conservative for pMMR patients in KEYNOTE-868.**

Table 3. Response rates with pembrolizumab (± CT) by MMR status

	pMMR	dMMR	
	KEYNOTE-868 (1L; pembrolizumab + CT)	**KEYNOTE-158 (2L+; pembrolizumab)**	**KEYNOTE-868 (1L; pembrolizumab + CT)**
OR rate	72.3%	50.6%	82.1%
CR rate	14.3%	15.7%	31.6%
PR rate	58.0%	34.9%	50.5%

Abbreviations: CR, complete response; CT, carboplatin + paclitaxel; MMR, mismatch repair; OR, objective response; PR, partial response.

b. *Similar HRQoL for dMMR and pMMR in KEYNOTE-775*

Secondly, Lorusso et al report HRQoL data from KEYNOTE-775 (pembrolizumab + lenvatinib in previously treated advanced/recurrent endometrial cancer) separately for the all comer (n=827) and pMMR (n=697) populations (84% of all comers population were pMMR).[22] The following observations are made:

- Across the four HRQoL measures reported, including EQ-5D-5L VAS, mean HRQoL at baseline and at 12 weeks was highly comparable between the all comer and pMMR cohorts, with a slight trend towards improved HRQoL in the pMMR cohort (Table 4).
- Within each cohort (all comers and pMMR), the difference in change from baseline (CFB) in HRQoL between the treatment arms was small and not statistically significant, despite improved OR and CR rates in the pembrolizumab + lenvatinib arm vs. the control arm (treatment of physician's choice [TPC]).
    - Similar findings were observed in KEYNOTE-868 pMMR patients (CFB to week 18 [i.e. to approximately 4 months and which is the start of the maintenance phase]; CS Document B Table 17). The mean time to response was 3.0 months and 2.9 months in the pembrolizumab and placebo arms, respectively. Therefore, if response rate materially affects HRQoL this would be reflected in the 18 week CFB data.
- These results indicate that response rate may not be a key determinant of HRQoL at a cohort level.

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Table 4. HRQoL results in KEYNOTE-775

	Pembrolizumab + lenvatinib			TPC			Difference in LS means (95% CI)[a]	*P*-value
	Baseline mean (SD)	Week 12 mean (SD)	CFB to week 12 LS mean (95% CI)	Baseline mean (SD)	Week 12 mean (SD)	CFB to week 12 LS mean (95% CI)		
EQ-5D-5L VAS								
All comers	73.70 (18.24)	70.37 (18.31)	-4.44 (-6.43, -2.46)	73.53 (18.91)	70.61 (19.25)	-6.79 (-8.98, -4.60)	2.35 (-0.44, 5.14)	0.0991
pMMR subgroup	74.08 (18.33)	70.23 (18.63)	-5.35 (-7.59, -3.11)	74.13 (18.61)	70.90 (19.77)	-7.41 (-9.85, -4.96)	2.06 (-1.09, 5.20)	0.1992
EORTC QLQ-C30 GHS/QoL								
All comers	65.74 (21.87)	60.56 (21.35)	−5.97 (−8.36, −3.58)	65.69 (22.71)	62.70 (21.08)	−6.98 (−9.63, −4.33)	1.01 (−2.28, 4.31)	0.5460
pMMR subgroup	66.56 (21.44)	60.94 (21.35)	-6.80 (-9.43, -4.17)	66.64 (22.43)	62.80 (21.67)	-7.96 (-10.86, -5.05)	1.16 (-2.49, 4.81)	0.5316
EORTC QLQ-C30 Physical Functioning								
All comers	78.68 (20.08)	71.51 (21.12)	−9.19 (−11.24, −7.14)	75.97 (20.88)	71.92 (21.78)	−9.10 (−11.37, −6.83)	−0.09 (−3.08, 2.90)	0.9537
pMMR subgroup	79.56 (19.21)	71.46 (21.64)	-10.42 (-12.65, -8.19)	76.58 (20.85)	72.81 (21.13)	-8.68 (-11.13, -6.23)	-1.74 (-4.99, 1.51)	0.2931
EORTC QLQEN24 Urological Symptoms								
All comers	14.89 (17.94)	12.91 (18.76)	−1.62 (−3.56, 0.31)	16.00 (19.32)	16.18 (18.33)	0.66 (−1.47, 2.79)	−2.29 (−5.03, 0.45)	0.1014
pMMR subgroup	14.89 (18.09)	12.37 (18.29)	-2.20 (-4.28, -0.12)	16.13 (19.79)	16.56 (19.29)	0.78 (-1.55, 3.11)	-2.98 (-5.96, 0)	0.0496

Abbreviations: CFB, change from baseline; CI, confidence interval; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire; EORTC QLQ-EN24, EORTC QLQ-Endometrial, 24 questions; EQ-5D-5L, EuroQoL 5 dimensions, 5 levels; GHS/QoL, global health status/quality of life; HRQoL, health-related quality of life; LS, least squares; SD, standard deviation; TPC, treatment of physician's choice; VAS, visual analog scale.
Source: Lorusso et al, 2024.[22]

c. Similar utilities for dMMR and pMMR in RUBY and KEYNOTE-B21

UK utilities by MMR status from other trials of first-line treatment for endometrial cancer are not available to MSD. However:

- Utilities from the RUBY trial, obtained using EQ-5D and valued using a US value set, showed slightly higher utility in the overall population (0.794 and 0.734 for progression-free and progressed disease, respectively) than in the dMMR subgroup (0.776 and 0.724) suggesting that HRQoL was slightly better in pMMR than dMMR disease (although note the US value set and small number of patients in the dMMR subgroup).[23]
- EQ-5D-3L utility values mapped from EQ-5D-5L scores collected in KEYNOTE-B21 (a trial of pembrolizumab plus adjuvant chemotherapy with or without radiotherapy in patients with newly diagnosed, high-risk endometrial cancer) have become available to MSD since the time of the original Company submission. Comparison of these utilities shows results for the 'Disease-free' health state are highly comparable between dMMR

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and pMMR cohorts (Table 5). Whilst this is a trial in an earlier stage of disease, and therefore the aim of treatment is to prevent recurrences rather than delay progression, these results provide evidence that there are no underlying differences in HRQoL between the MMR cohorts.

Table 5. EQ-5D-3L utilities from KEYNOTE-B21

Health state	dMMR			pMMR		
	n	Mean	95% CI	n	Mean	95% CI
Disease-free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ongoing treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Completed or discontinued treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease recurrence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Locoregional	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Distant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval.
Pooled EQ-5D-5L UK utilities mapped to EQ-5D-3L using mapping algorithm from Hernandez Alava et al, 2023,[24].
† Very few patients in the dMMR group of KEYNOTE-B21 had disease recurrence by the last database lock, and therefore utility values for the Disease Recurrence health state in the dMMR group may be unreliable.

d. *Progression-free health state mostly comprised of responders in the long-term*

Finally, it is helpful to consider the contribution of responders to the health states used in the model. Ultimately, patients who do not have a response to treatment (with immunotherapy or CT) will progress rapidly. In addition, many patients with a partial response will also progress before long (the median duration of response in the KEYNOTE-868 [NRG-GY018] pMMR group was 8.1 months in the pembrolizumab + CT arm and 6.4 months in the CT arm). As such, the proportion of patients in the progression-free state who have not had a response will be relatively small and will decrease so that, over time, the progression-free state will increasingly be comprised of responders with durable responses. Consequently, given that any patients remaining in the progression-free state after the first year (for the remainder of the 35-year time horizon) will primarily be patients with long-term, durable responses, it would be reasonable for the utility value used for the progression-free state to represent responders. So, even if the utilities from KEYNOTE-158 do disproportionately represent patients who had a good response to immunotherapy (on account of being collected from dMMR patients), this should still be reflective of pMMR patients who remain progression-free in the long-term as these are also patients who had a good response.

Utility values used in the model

1. Utilities from KEYNOTE-B21 are more representative of 1L setting

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The definition of the 'Disease recurrence' health state from KEYNOTE-B21 is largely aligned with that of the 'Progression-free' health state in the current model – i.e., first-line treatment in the advanced setting. The 'Disease recurrence' utilities for dMMR are based on a very small number of patients and lack face validity against the 'Disease-free' utilities. However, in the pMMR group the utility for the 'Disease recurrence' health state in KEYNOTE-B21 is based on over 100 patients and does have face validity vs the 'Disease-free' utility.

- The mean utility for pMMR 'Disease recurrence' was [redacted]. This is higher than the utility taken from second-line dMMR patients in KEYNOTE-158 which was used for MSD's base case in the submission ([redacted]), suggesting that the KEYNOTE-158 utilities are conservative.

In addition:

- MSD has identified an additional publication reporting a baseline UK utility of 0.75 for the all comer population in KEYNOTE-775 (second-line endometrial cancer).[25]
- Whilst the actual utility values from the DUO-E trial used in the NICE ID6317 appraisal of another immunotherapy for first-line endometrial cancer are redacted, it is clear from the committee papers that:[2]
  - the DUO-E utilities are higher than the KEYNOTE-158 utilities, and;
  - the same utilities were used for dMMR and pMMR. The EAG for that appraisal cite clinical expert opinion that there is no clinical reason why HRQoL would differ by MMR status.

Collectively, this evidence supports the assertion that the utilities sourced from KEYNOTE-158 are conservative for this first-line indication, regardless of MMR status.

2. <u>Base case progression-free utility updated to use KEYNOTE-B21</u>

The evidence suggests that the utility values from KEYNOTE-158 dMMR patients used in MSD's original base case underestimate the HRQoL of patients in the first-line progression-free state for pMMR. Given the recently available 'Disease recurrence' utility data from KEYNOTE-B21 pMMR cohort are based on a larger sample size than the utilities from KEYNOTE-158 and better reflect the population (i.e. treatment line/setting) under consideration, this value is used for the 'Progression-free' state in MSD's updated base case.

This is the best available data to reflect the population in the decision problem. The KEYNOTE-158 progressed disease utility is retained for the 'Progressed' health state, in line with the committee's stated preference in the DG. Based on the evidence presented above, the same utilities are applied in both dMMR and pMMR cohort analyses.

A series of scenario analyses are also presented, exploring alternative sources and assumptions for the Progression-free and Progressed health states (Table 6 and Appendix 1). These analyses demonstrate that the choice of utility values has a small impact on the cost-effectiveness conclusions.

Table 6. Utility values explored in scenario analyses

Scenario	Progression-free	Progressed	Notes
Base case			
KEYNOTE-B21 & KEYNOTE-158 (2L EC)	[redacted]	[redacted]†	**Updated base case**

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				PF: 1L EC, pMMR subgroup (KN-B21) PD: 2L+ MSI-H/dMMR, 1 prior line (2L) EC subgroup (KN-158) EQ-5D-3L, UK values Source: MSD Data on File
	Scenario analyses			
	KEYNOTE-158 (2L EC)	[redacted]	[redacted]	**Original base case** 2L+ MSI-H/dMMR, 1 prior line EC subgroup EQ-5D-3L, UK values Source: MSD Data on File
	KEYNOTE-B21 & KEYNOTE-158 (2L+ EC)	[redacted]	0.720	PF: 1L EC, pMMR subgroup (KN-B21) PD: 2L+ MSI-H/dMMR, EC subgroup (KN-158) EQ-5D-3L, UK values Source: MSD Data on File; McCarthy, 2024[26]
	KEYNOTE-775	0.736	0.700	2L EC, All comers EQ-5D-5L, Australian values Source: PBAC review of KEYNOTE-775[27]
	RUBY	0.794	0.734	1L EC, All comers EQ-5D-5L, US values Source: Coleman, 2025[23]

Abbreviations: 1L, first-line; 2L, second-line; dMMR, mismatch repair deficient; EC, endometrial cancer; MSI-H, microsatellite instability high; PBAC, Pharmaceutical Benefits Advisory Committee.
† Utilities for progressed disease not available from KEYNOTE-B21 trial, therefore utility from KEYNOTE-158 continues to be used.

Summary

In summary, the evidence suggests that although response rates do differ by MMR status, this does not have a material impact on HRQoL at a cohort level. The impact of progression on HRQoL is already incorporated into the model. Consequently**, it should be appropriate to use the same utilities for modelling dMMR and pMMR disease**, and the KEYNOTE-158 utilities may still be conservative. The base case has been updated to reflect newly available data from KEYNOTE-B21 collected from patients with recurrent pMMR disease. A range of scenario analyses demonstrate that the source of utility value does not have a meaningful impact on the cost-effectiveness of pembrolizumab + CT in this indication.

6. Resource use estimates

6	**Resource use estimates in the economic model (DG Section 3.11)** In the DG, it is stated that the committee's preference is to use progression-free resource use estimates from the EAG's clinical expert, but that an analysis assuming greater resource use for

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	those having treatment in the pembrolizumab + CT arm to reflect a 3-weekly (Q3W) cycle length rather than 6-weekly (Q6W) would be welcomed. To inform this consultation and ensure the resource use estimates are reflective of clinical practice, MSD collected additional insights regarding the resource use over time for patients who remain progression-free (Appendix 4, Table 21), and reviewed the insights from the previous advisory board and EAG experts. The progression-free resource use estimates provided by the EAG's clinical expert are in fact aligned with the estimates provided by MSD's clinical experts at the advisory board held in July 2024,[28] and the newly-collected insights. These collated resource use assumptions are summarised as follows: • *O- treatment*, patients in both arms would have a blood test and outpatient visit with each cycle of treatment (Q3W while on chemotherapy (± pembrolizumab); Q6W while on pembrolizumab monotherapy), and a CT scan every 12 weeks (3 months). • *Once off-treatment*, patients in both arms would have a CT scan, blood test and outpatient visit every 12 weeks (3 months) for the first 2 years. From year 3 onwards, most clinicians (8/11 experts consulted) would reduce the frequency to every 26 weeks (6 months). • *Once disease has progressed*, blood tests and outpatient visits would be approximately every 9 weeks (2 months). However, the approach to applying resource use and costs in the progression-free health state was incorrectly applied in the previously submitted model and so the model did not appropriately reflect the expected resource use requirements in either arm. It appears that the EAG's implementation of resource use reflecting their clinical expert's advice was also incorrectly applied. The corrected resource use assumptions, which align with MSD's advisory board, the additional clinical expert insights obtained by MSD during consultation, the EAG's clinical experts, and the committee's preferences, are presented in Table 7. **The model has been corrected to reflect these resource use schedules and these corrections are therefore incorporated in MSD's updated base case analyses.** A scenario analysis whereby regular monitoring activities for the progression-free state are stopped after 5 years (260 weeks) is also presented. This is based on clinical expert insights shared with MSD that patients with a CR might be discharged at 5 years if still progression-free. It is likely that most patients who remain progression-free at 5 years had a CR. This resulted in a slightly lower ICER of [redacted]/QALY (7% decrease) for dMMR and [redacted]/QALY for pMMR (4% decrease). With regards to the requested scenario analysis assuming greater resource use for patients in the pembrolizumab + CT arm to reflect a Q3W (rather than Q6W) cycle length in the pembrolizumab maintenance phase, the wording in section 4.2 of the SmPC regarding the posology for this specific indication is "*For first-line treatment of primary advanced or recurrent endometrial carcinoma, the recommended dose of KEYTRUDA is 200 mg every 3 weeks for 6 cycles in combination with chemotherapy, followed by KEYTRUDA 400 mg every 6 weeks for up to 14 cycles as monotherapy*".[29] This explicitly states the recommended dosing schedule for this indication, which differs to other pembrolizumab indications where the dosing schedule is not specified in the SmPC. Whilst this is not mandatory, it suggests that for this first-line endometrial cancer indication maintenance pembrolizumab monotherapy would preferably be administered at 400 mg Q6W. For completeness, a scenario analysis assuming Q3W maintenance dosing (with associated blood tests and outpatient visits) resulted in a slightly higher ICER of [redacted]/QALY (8% increase) for dMMR and [redacted]/QALY for pMMR (5% increase).

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Table 7. Corrected resource use assumptions in updated economic analysis

Health state	Resource	Frequency	Frequency per week (applied in model)	Source
Pembrolizumab + CT				
PFS (On treatment): pembrolizumab + CT	Computed tomography scan	12 wks (3 mo)	0.08	MSD advisory board;[28] EAG clinical expert[30]
	Outpatient visit	*Cycle 0-17*: 3 wks *Cycle 18-104*: 6 wks	0.33	
	Blood test		0.17	
PFS (Off treatment): pembrolizumab + CT	Computed tomography scan	*Cycle 0-104*: 12 wks (3 mo) *Cycle 105+:* 26 wks (6 mo)	0.08	MSD advisory board;[28] EAG clinical expert;[30] MSD clinical expert insights (Appendix 4)
	Outpatient visit		0.04	
	Blood test			
CT				
PFS (On treatment): CT	Computed tomography scan	12 wks (3 mo)	0.08	MSD advisory board;[28] EAG clinical expert[30]
	Outpatient visit	*Cycle 0-17*: 3 wks	0.33	
	Blood test			
PFS (Off treatment): CT	Computed tomography scan	*Cycle 0-104*: 12 wks (3 mo) *Cycle 105+:* 26 wks (6 mo)	0.08	MSD advisory board;[28] EAG clinical expert;[30] MSD clinical expert insights (Appendix 4)
	Outpatient visit		0.04	
	Blood test			

Abbreviations: CT, carboplatin + paclitaxel; mo, months; PFS, progression-free survival.

7. Starting age

7	**Starting age in the economic model (DG Section 3.8)** In the DG, the committee requested an update to the model that reflects the individual starting ages of people with dMMR and pMMR advanced or recurrent endometrial cancer. After the first committee meeting, the Cancer Drugs Fund (CDF) lead shared data on the average age of people who received specific treatments for endometrial cancer in the NHS, by indication, which can be used to address this request. Note that while medians are stated in the DG, health economic analysis typically uses mean values for model inputs and therefore the means provided by the CDF lead are considered in MSD's response.

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	dMMR The data demonstrated that the mean age of all patients who have been treated with dostarlimab + CT for dMMR endometrial cancer previously untreated in the advanced/metastatic setting in the UK NHS (via the CDF) since approval is **65.4 years**.[31] The mean age at baseline of dMMR patients in the KEYNOTE-868 (NRG-GY018) trial was **65.7 years,** which is highly concordant with the real-world data. The population for the dostarlimab indication is exactly aligned with the subgroup population under consideration in the current technology appraisal. Therefore, the patients receiving dostarlimab + CT via the CDF in current practice should be considered representative of the dMMR patients who would be eligible for pembrolizumab + CT in the UK NHS. **Consequently, the mean age for the dMMR population, sourced from the UK NHS data, is used in MSD's updated base case for the dMMR subgroup.** ***pMMR*** For pMMR, there is no information in the UK NHS data provided that precisely relates to the "previously untreated in the advanced/metastatic setting" pMMR population under consideration. The most informative available options are: • "Dostarlimab + CT for dMMR endometrial cancer previously untreated in the advanced/metastatic setting", as described above: mean age **65.4 years**. This is the closest match in terms of disease setting but refers specifically to dMMR disease. • "Pembrolizumab plus lenvatinib in patients previously treated with platinum-containing therapy given in any setting": mean age **67.54 years**. Within this population, 91.6% of recipients had pMMR disease, however this indication refers to patients who have been previously treated with platinum-containing therapy (i.e. it is second- or later-line therapy). It is therefore to be expected that these patients are slightly older than patients who have not previously received treatment in the advanced/metastatic setting as they are only eligible for treatment after progressing on first-line therapy. The mean age at baseline of pMMR patients in the KEYNOTE-868 (NRG-GY018) trial was **65.4 years,** which aligns with the real-world mean age of patients who had dostarlimab + CT. The mean baseline ages of patients enrolled in KEYNOTE-868 (NRG-GY018) are therefore highly comparable for dMMR and pMMR patients (65.7 years and 65.4 years, respectively) indicating that there is no meaningful difference in the average age of patients with dMMR vs pMMR disease. Consequently, MSD considers that the baseline mean age observed for dMMR patients treated with dostarlimab + CT in the UK NHS and pMMR patients in the trial (65.4 years) is the most appropriate value to model the pMMR subgroup. This is therefore used in MSD's updated base case for the pMMR subgroup. The EAG are aligned with MSD on this approach. A scenario analysis using the mean age of patients treated with pembrolizumab + lenvatinib in the UK NHS (67.54 years) is also presented for the pMMR analysis. This increases the ICER by approximately 2%, indicating that uncertainty regarding starting age has a minimal impact on the cost-effectiveness.

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Insert extra rows as needed

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Appendix

1 Updated cost-effectiveness results

Updated base case, PSA and scenario results are presented in this Appendix. All results are based on the PAS price of pembrolizumab but use the list price of lenvatinib.

1.1 dMMR

1.1.1 Base case

Table 8 shows the cost-effectiveness results for pembrolizumab + CT versus CT, for the dMMR cohort. The results show that pembrolizumab + CT is estimated to offer greater health benefits compared to CT alone, with an ICER of [redacted] per QALY gained.

Table 8. Base case results: dMMR

Technologies	Total costs, £	Total LYG	Total QALYs	Inc costs, £	Inc LYG	Inc QALYs	ICER (£/QALY)
Pembrolizumab + CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2.24	[redacted]
CT	[redacted]	5.01	[redacted]	-	-	-	-

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

1.1.2 Probabilistic sensitivity analysis

The results of the PSA based on 1,000 iterations are presented in Table 9, showing a probabilistic ICER of [redacted] per QALY gained. Figure 5 shows the cost-effectiveness acceptability curve. At a willingness to pay of £30,000 and £20,000 the probability that pembrolizumab + CT is cost-effective is [redacted] and [redacted], respectively. Figure 6 presents the cost-effectiveness plane for pembrolizumab + CT

Table 9. Mean probabilistic base case results: dMMR

Technologies	Total costs, £	Total LYG	Total QALYs	Inc costs, £	Inc LYG	Inc QALYs	ICER (£/QALY)
Pembrolizumab + CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2.06	[redacted]
CT	[redacted]	5.02	[redacted]	-	-	-	-

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

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Figure 5. Cost effectiveness acceptability curve, pembrolizumab + CT versus CT: dMMR

[redacted]

Figure 6. Cost-effectiveness plane, pembrolizumab + CT versus CT: dMMR

[redacted]

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1.1.3 Scenario analyses

Results from a range of plausible scenarios for the dMMR population are presented in Table 10.

Table 10. Scenario analysis results: dMMR

#	Category	Scenario	Description/ rationale	Inc. costs	Inc QALYs	ICER	% change
	Base case	-	-	[redacted]	**2.24**	[redacted]	-
1	Utilities	PF&PD: KEYNOTE-158, 1 prior line (2L) EC	1 prior line (2L) EC, dMMR (PF, [redacted]; PD, [redacted])	[redacted]	2.14	[redacted]	4%
2		PF: KEYNOTE-B21, disease recurrence PD: KEYNOTE-158, 2L+ EC	PF: Recurrent EC, pMMR PD: 2L+ EC, dMMR (McCarthy,2024)[26] (PF, [redacted]; PD, 0.720)	[redacted]	2.22	[redacted]	1%
3		PF&PD: KEYNOTE-775, PBAC	2L EC, All comer (Australia) (PF, 0.736; PD, 0.700)	[redacted]	2.17	[redacted]	3%
4		PF&PD: RUBY	1L EC, All comer (US) (Coleman, 2025)[23] (PF, 0.794; PD, 0.734)	[redacted]	2.31	[redacted]	-3%
5	Baseline age	Mean baseline age in KEYNOTE-868	Mean age: 65.7 years (dMMR cohort in KEYNOTE-868 trial)	[redacted]	2.22	[redacted]	1%
6	Resource use	200mg Q3W dosing schedule for pembrolizumab in maintenance phase	Committee request. Includes Q3W blood tests & outpatient visits	[redacted]	2.24	[redacted]	8%
7		Resource use in the progression-free state capped at 5-years	Based on clinical opinion that patients with a CR might be discharged at 5-years if still progression-free	[redacted]	2.24	[redacted]	-7%

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#	Category	Scenario	Description/ rationale	Inc. costs	Inc QALYs	ICER	% change
8	Treatment effect waning	TEW applied to: • Timepoint: 7-9 years • Patients: No-CR (68.4%)	Timepoint based on conservative scenarios in TA914[16] & TA997[17] Assume TEW applies **only to patients without a CR**, as in TA997[17]	[redacted]	1.68	[redacted]	32%
9		TEW applied to: • Timepoint: 7-9 years • Patients: All (100%)	Timepoint based on conservative scenarios in TA914[16] & TA997[17] Assume waning applies to **all** patients	[redacted]	1.38	[redacted]	59%
10	OS extrapolations	• Pembro + CT: **Log-normal** • CT: **Gamma**	More optimistic pembro + CT, more pessimistic CT; to more closely reflect committee preferred curves in NICE ID6426	[redacted]	3.23	[redacted]	-28%
11		• Pembro + CT: Log-logistic • CT: **Log-logistic**	To explore more optimistic long-term OS estimates for CT, including naturally converging hazards	[redacted]	1.69	[redacted]	25%
12	Subsequent treatment	Treatment mix from KEYNOTE-868 trial adjusted to reflect clinical expert opinion from ad board (as in submission)	Adjustments to treatment mix of non-immunotherapy regimens to reflect previously collected clinical opinion regarding use in UK clinical practice, to align with the original Company submission	[redacted]	2.24	[redacted]	8%

Abbreviations: 2L, second-line; CR, complete response; CT, chemotherapy; EC, endometrial cancer; OS, overall survival; PD, progressed disease; PF, progression-free; TEW, treatment effect waning.

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1.2 pMMR

1.2.1 Base case

Table 8 shows the cost-effectiveness results for pembrolizumab + CT versus CT, for the pMMR cohort. The results show that pembrolizumab + CT is estimated to offer greater health benefits compared to CT alone, with an ICER of [redacted] per QALY gained.

Table 11. Base case results: pMMR

Technologies	Total costs, £	Total LYG	Total QALYs	Inc costs, £	Inc LYG	Inc QALYs	ICER (£/QALY)
Pembrolizumab + CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.21	[redacted]
CT	[redacted]	2.55	[redacted]	-	-	-	-

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

1.2.2 Probabilistic sensitivity analysis

The results of the PSA based on 1,000 iterations are presented in Table 9, showing a probabilistic ICER of [redacted] per QALY gained. Figure 7 shows the cost-effectiveness acceptability curve. At a willingness to pay of £30,000 and £20,000 the probability that pembrolizumab + CT is cost-effective is [redacted]% and [redacted]%, respectively. Figure 8 presents the cost-effectiveness plane for pembrolizumab + CT.

Table 12. Mean probabilistic base case results: pMMR

Technologies	Total costs, £	Total LYG	Total QALYs	Inc costs, £	Inc LYG	Inc QALYs	ICER (£/QALY)
Pembrolizumab + CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.16	[redacted]
CT	[redacted]	2.54	[redacted]	-	-	-	-

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Figure 7. Cost effectiveness acceptability curve, pembrolizumab + CT versus CT: pMMR

[redacted]

Figure 8. Cost-effectiveness plane, pembrolizumab + CT versus CT: pMMR

[redacted]

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1.2.3 Scenario analyses

Results from a range of plausible scenarios for the pMMR cohort are presented in Table 13.

Table 13. Scenario analysis results: pMMR

#	Category	Scenario	Description/ rationale	Inc. costs	Inc QALYs	ICER	% change
	Base case	**-**		[redacted]	**1.21**	[redacted]	
1	Utilities	PF&PD: KEYNOTE-158, 1 prior line (2L) EC	1 prior line (2L) EC, dMMR (PF, [redacted]; PD, [redacted])	[redacted]	1.18	[redacted]	3%
2		PF: KEYNOTE-B21, disease recurrence PD: KEYNOTE-158, 2L+ EC	PF: Recurrent EC, pMMR PD: 2L+ EC, dMMR (McCarthy,2024)[26] (PF, [redacted]; PD, 0.720)	[redacted]	1.22	[redacted]	-1%
3		PF&PD: KEYNOTE-775, PBAC	2L EC, All comer (Australia) (PF, 0.736; PD, 0.700)	[redacted]	1.19	[redacted]	2%
4		PF&PD: RUBY	1L EC, All comer (US) (Coleman, 2025)[23] (PF, 0.794; PD, 0.734)	[redacted]	1.28	[redacted]	-5%
5	Baseline age	Mean baseline age of patients receiving 2L pembrolizumab + lenvatinib in UK practice	Mean age: 67.54 years (NHS England data)	[redacted]	1.19	[redacted]	2%
6	Resource use	200mg Q3W dosing schedule for pembrolizumab in maintenance phase	Committee request. Includes Q3W blood tests & outpatient visits	[redacted]	1.21	[redacted]	5%

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#	Category	Scenario	Description/ rationale	Inc. costs	Inc QALYs	ICER	% change
7		Resource use in the progression-free state capped at 5-years	Based on clinical opinion that patients with a CR might be discharged at 5-years if still progression-free	[redacted]	1.21	[redacted]	-4%
8	Treatment effect waning	TEW applied to: • Timepoint: 7-9 years Patients: No-CR (85.7%)	Timepoints based on conservative scenarios in TA914[16] & TA997[17] Assume TEW applies **only to patients without a CR**, as in TA997[17]	[redacted]	0.84	[redacted]	42%
9		TEW applied to: • Timepoint: 7-9 years • Patients: All (100%)	Timepoints based on conservative scenarios in TA914[16] & TA997[17] Assume waning applies to **all patients**	[redacted]	0.77	[redacted]	53%
10	OS extrapolations	• Pembro + CT: Log-logistic • CT: **2-knot odds**	To reflect more optimistic long-term OS estimates (flatter tail) in the CT arm, including naturally converging hazards	[redacted]	0.93	[redacted]	28%
11	Subsequent treatment	Treatment mix in CT arm adjusted to: (a) IO combined: Pembrolizumab monotherapy market share added to pembrolizumab + lenvatinib	Pembrolizumab monotherapy not available in UK practice. Assumed patients who had monotherapy in the trial would get combination therapy in practice.	[redacted]	1.21	[redacted]	-14%
12		Treatment mix in CT arm adjusted to: (c) IO redistributed to non-IO	Pembrolizumab monotherapy not available in UK practice. Monotherapy market share proportionally redistributed across	[redacted]	1.21	[redacted]	24%

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#	Category	Scenario	Description/ rationale	Inc. costs	Inc QALYs	ICER	% change
			all other 2L non-immunotherapy treatments.				

Abbreviations: 2L, second-line; CR, complete response; CT, chemotherapy; EC, endometrial cancer; IO, immunotherapy; OS, overall survival; PD, progressed disease; PF, progression-free; TEW, treatment effect waning.

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1.3 All comer

1.3.1 Base case

Table 8 shows the cost-effectiveness results for pembrolizumab + CT versus CT, for the all comer population. The results show that pembrolizumab + CT is estimated to offer greater health benefits compared to CT alone, with an ICER of [redacted] per QALY gained.

Table 14. Base case results: All comer

Technologies	Total costs, £	Total LYG	Total QALYs	Inc costs, £	Inc LYG	Inc QALYs	ICER (£/QALY)
Pembrolizumab + CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.39	[redacted]
CT	[redacted]	3.79	[redacted]	-	-	-	-

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

1.3.2 Probabilistic sensitivity analysis

The results of the PSA based on 1,000 iterations are presented in Table 9, showing a probabilistic ICER of [redacted] per QALY gained. Figure 9 shows the cost-effectiveness acceptability curve. At a willingness to pay of £30,000 and £20,000 the probability that pembrolizumab + CT is cost-effective is [redacted]% and [redacted]%, respectively. Figure 10 presents the cost-effectiveness plane for pembrolizumab + CT.

Table 15. Mean probabilistic base case results: All comer

Technologies	Total costs, £	Total LYG	Total QALYs	Inc costs, £	Inc LYG	Inc QALYs	ICER (£/QALY)
Pembrolizumab + CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.38	[redacted]
CT	[redacted]	3.76	[redacted]	-	-	-	-

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Figure 9. Cost effectiveness acceptability curve, pembrolizumab + CT versus CT: All comer

[redacted]

Figure 10. Cost-effectiveness plane, pembrolizumab + CT versus CT: All comer

[redacted]

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1.3.3 Scenario analyses

Results from a range of plausible scenarios for the all comer population are presented in Table 16.

Table 16. Scenario analysis results: All comer

#	Category	Scenario	Description/ rationale	Inc. costs	Inc QALYs	ICER	% change
	Base case	**-**		[redacted]	**1.39**	[redacted]	**-**
1	Utilities	PF&PD: KEYNOTE-158, 1 prior line (2L) EC	1 prior line (2L) EC, dMMR (PF, [redacted]; PD, [redacted])	[redacted]	1.33	[redacted]	4%
2		PF: KEYNOTE-B21, disease recurrence PD: KEYNOTE-158, 2L+ EC	PF: Recurrent EC, pMMR PD: 2L+ EC, dMMR (McCarthy,2024)[26] (PF, [redacted]; PD, 0.720)	[redacted]	1.38	[redacted]	1%
3		PF&PD: KEYNOTE-775, PBAC	2L EC, All comer (Australia) (PF, 0.736; PD, 0.700)	[redacted]	1.35	[redacted]	3%
4		PF&PD: RUBY	1L EC, All comer (US) (Coleman, 2025)[23] (PF, 0.794; PD, 0.734)	[redacted]	1.48	[redacted]	-6%
5	Baseline age	Mean baseline age of patients receiving 2L pembrolizumab + lenvatinib in UK practice	Mean age: 67.54 years (NHS England data)	[redacted]	1.35	[redacted]	3%
6	Resource use	200mg Q3W dosing schedule for pembrolizumab in maintenance phase	Committee request. Includes Q3W blood tests & outpatient visits	[redacted]	1.39	[redacted]	6%

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#	Category	Scenario	Description/ rationale	Inc. costs	Inc QALYs	ICER	% change
7		Resource use in the progression-free state capped at 5-years	Based on clinical opinion that patients with a CR might be discharged at 5-years if still progression-free	[redacted]	1.39	[redacted]	-6%
8	Treatment effect waning	TEW applied to: • Timepoint: 7-9 years Patients: No-CR (80.6%)	Timepoints based on conservative scenarios in TA914[16] & TA997[17] Assume TEW applies **only to patients without a CR**, as in TA997[17]	[redacted]	1.18	[redacted]	18%
9		TEW applied to: • Timepoint: 7-9 years • Patients: All (100%)	Timepoints based on conservative scenarios in TA914[16] & TA997[17] Assume waning applies to **all patients**	[redacted]	1.12	[redacted]	24%
10	OS extrapolations	• Pembro + CT: 3-knot odds • CT: **Generalised gamma**	As per submission: To explore more pessimistic long-term OS estimates in the CT arm	[redacted]	1.67	[redacted]	-15%
11		• Pembro + CT: 3-knot odds • CT: **Log-normal**	As per submission: To explore more optimistic long-term OS estimates in the CT arm	[redacted]	1.09	[redacted]	24%
12		• Pembro + CT: **2P log-normal** • CT: Log-logistic	As per submission: To explore more optimistic long-term OS estimates for pembrolizumab + CT	[redacted]	1.80	[redacted]	-20%
13		• Pembro + CT: **2-knot odds** • CT: Log-logistic	As per submission: To explore more conservative long-term OS estimates for pembrolizumab + CT	[redacted]	1.20	[redacted]	14%

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#	Category	Scenario	Description/ rationale	Inc. costs	Inc QALYs	ICER	% change
14	Subsequent treatment	Treatment mix in CT arm adjusted to: (a) IO combined: Pembrolizumab monotherapy market share added to pembrolizumab + lenvatinib	Pembrolizumab monotherapy not available in UK practice. Assumed patients who had monotherapy in the trial would get combination therapy in practice.	[redacted]	1.39	[redacted]	-8%
15		Treatment mix in CT arm adjusted to: (c) IO redistributed to non-IO	Pembrolizumab monotherapy not available in UK practice. Monotherapy market share proportionally redistributed across all other 2L non-immunotherapy treatments.	[redacted]	1.39	[redacted]	14%

Abbreviations: 2L, second-line; CR, complete response; CT, chemotherapy; EC, endometrial cancer; OS, overall survival; PD, progressed disease; PF, progression-free; TEW, treatment effect waning.

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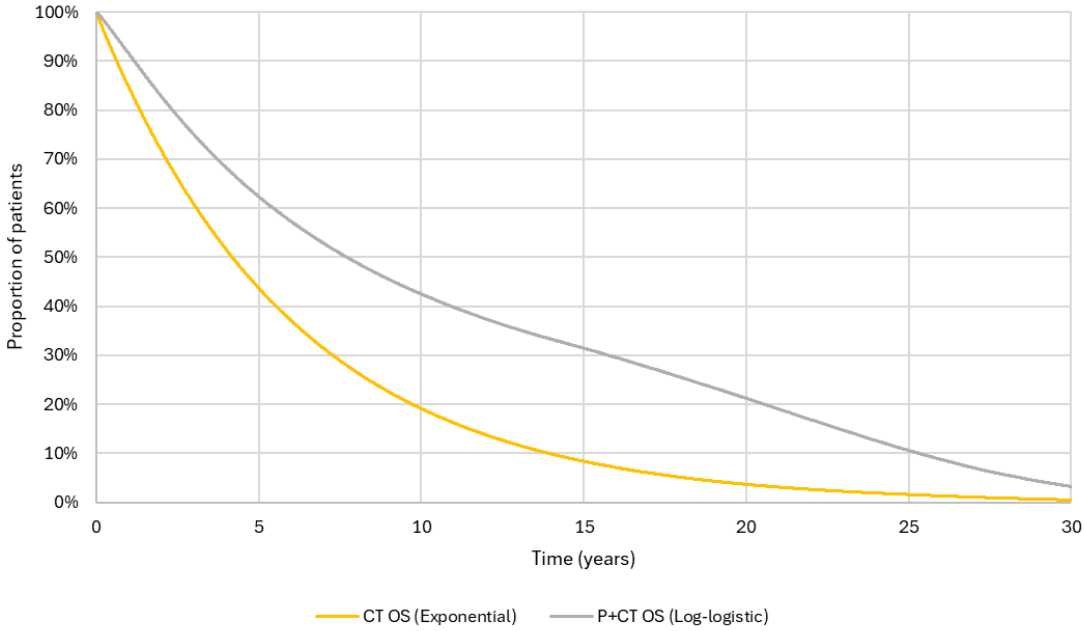
2 Curve extrapolations and selection

2.1 dMMR

2.1.1 Base case

Figure 11: OS extrapolation for CT and pembrolizumab + CT – dMMR base case



Key: CT, chemotherapy; OS, overall survival; P+CT, pembrolizumab + chemotherapy; PFS, progression free survival;

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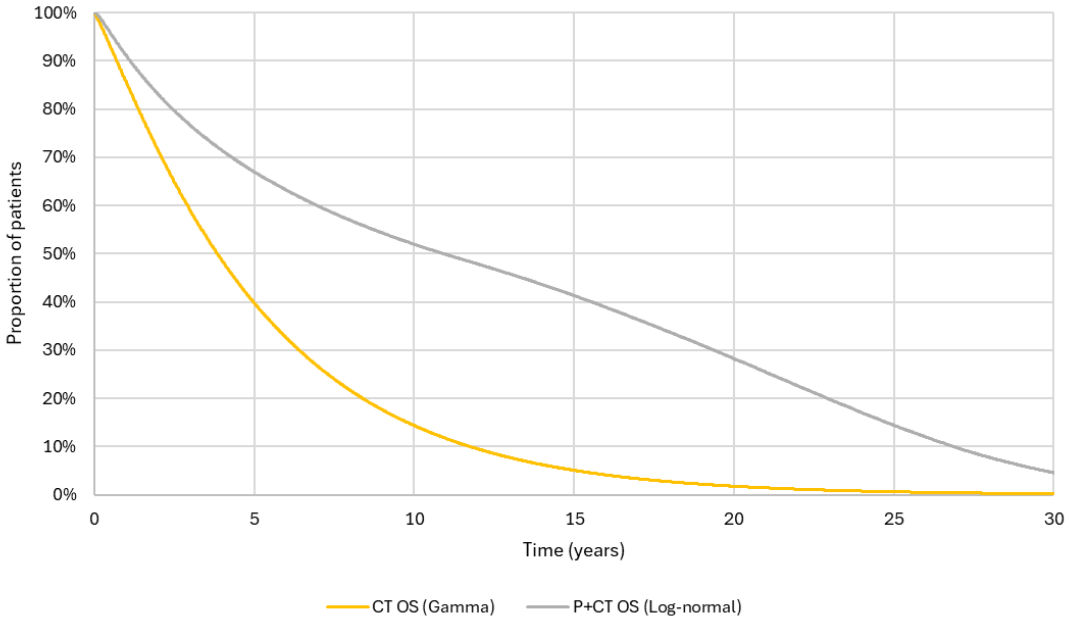
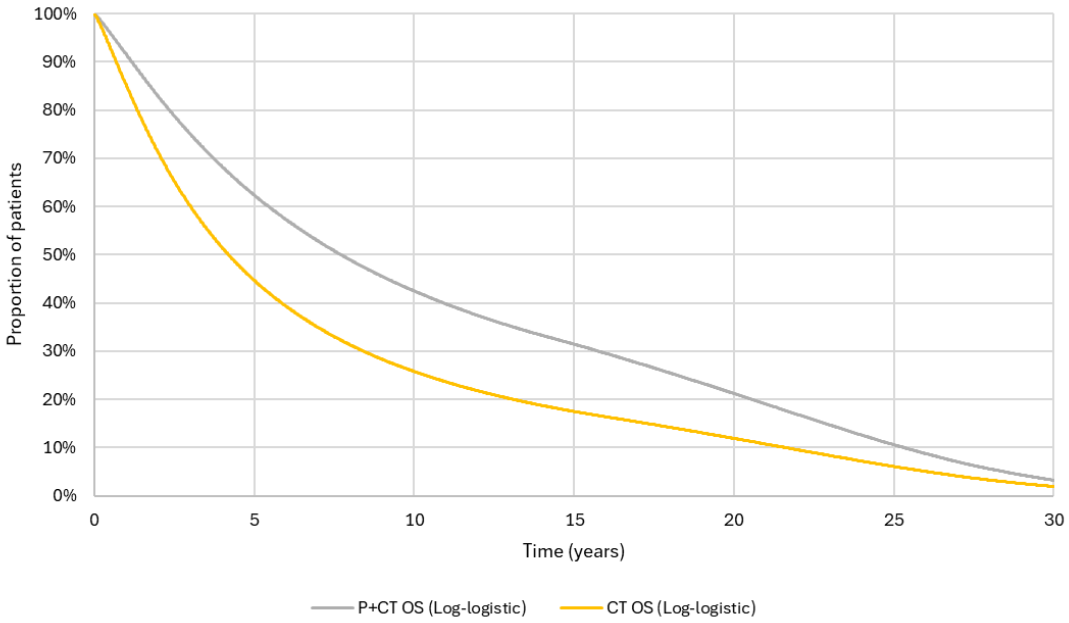
2.1.2 Scenario analyses

Figure 12: OS extrapolation for CT and pembrolizumab + CT – dMMR scenario 10



Key: CT, chemotherapy; OS, overall survival; P+CT, pembrolizumab + chemotherapy; PFS, progression free survival

Figure 13: OS extrapolation for CT and pembrolizumab + CT – dMMR scenario 11



Key: CT, chemotherapy; OS, overall survival; P+CT, pembrolizumab + chemotherapy; PFS, progression free survival

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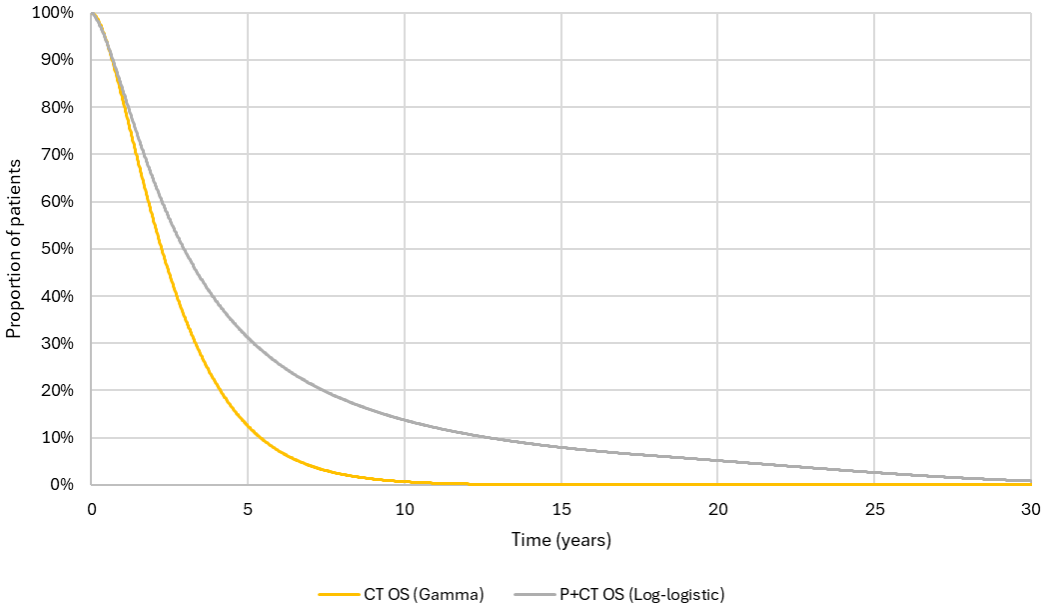
2.2 pMMR

2.2.1 Base case

Figure 14: OS extrapolation for CT and pembrolizumab + CT – pMMR base case



Key: CT, chemotherapy; OS, overall survival; P+CT, pembrolizumab + chemotherapy; PFS, progression free survival

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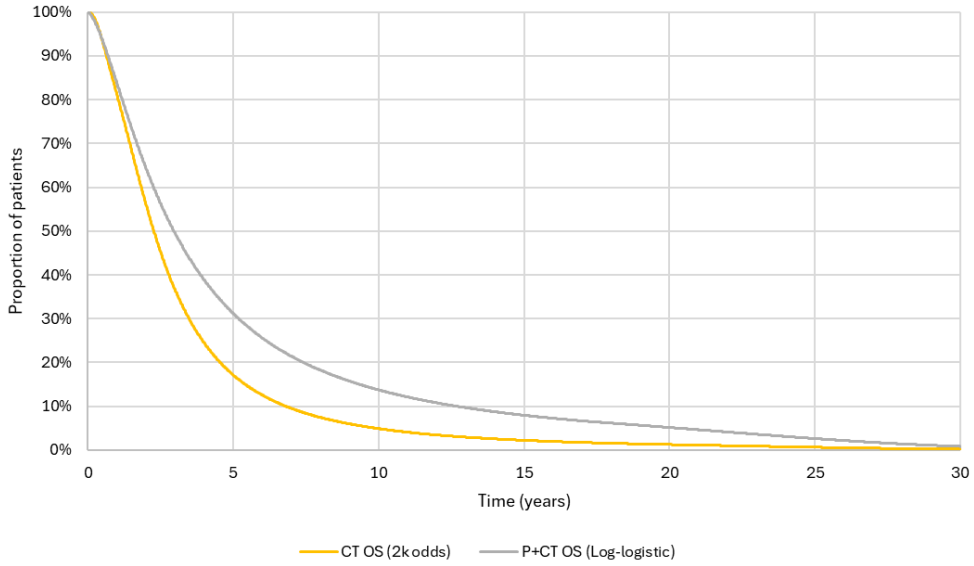
2.2.2 Scenario analysis

Figure 15: OS extrapolation for CT and pembrolizumab + CT – pMMR scenario 10



Key: CT, chemotherapy; OS, overall survival; P+CT, pembrolizumab + chemotherapy; PFS, progression free survival; 2k, 2-knot.

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3 Subsequent treatments

Table 17. Subsequent treatments used in KEYNOTE-868 (NRG-GY018) adjusted for use in model: dMMR

dMMR	Pembrolizumab + CT (IO redistributed)†	CT (unadjusted)
Carboplatin	[redacted]	[redacted]
Carboplatin + paclitaxel	[redacted]	[redacted]
Dostarlimab	[redacted]	[redacted]
Doxorubicin	[redacted]	[redacted]
Letrozole	[redacted]	[redacted]
Megestrol	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]
Pembrolizumab + lenvatinib	[redacted]	[redacted]
Radiotherapy	[redacted]	[redacted]
No active treatment	[redacted]	[redacted]
% of 2L-treated patients who get IO	-	[redacted]

Abbreviations: CT, carboplatin + paclitaxel.
Data represent first subsequent treatment received amongst patients who progressed in each arm of the KEYNOTE-868 (NRG-GY018) trial. Treatments recorded as subsequent treatments that are unavailable in practice or not used in the UK (e.g. investigational agents) have already been removed.
† Retreatment with immunotherapy in the pembrolizumab + CT is not permitted therefore market shares for immunotherapies set to 0% and shares for other treatments proportionally adjusted.

Table 18. Subsequent treatments used in KEYNOTE-868 (NRG-GY018) adjusted for use in model: pMMR

pMMR	Pembrolizumab + CT (IO redistributed)†	CT			
		Unadjusted	(a) IO combined‡	(b) IO mono redistributed§	(c) IO mono redistributed to non-IO¶
Carboplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin + paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dostarlimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Doxorubicin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Letrozole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Megestrol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + lenvatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No active treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% of 2L-treated patients who get IO	-	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 2L, second line; CT, carboplatin + paclitaxel; IO, immunotherapy.
Data represent first subsequent treatment received amongst patients who progressed in each arm of the KEYNOTE-868 (NRG-GY018) trial. Treatments recorded as subsequent treatments that are unavailable in practice or not used in the UK (e.g. investigational agents) have already been removed.
† Retreatment with immunotherapy in the pembrolizumab + CT is not permitted therefore market shares for immunotherapies set to 0% and shares for other treatments proportionally adjusted.
‡ Pembrolizumab monotherapy is not available in UK practice for patients with pMMR disease – pembrolizumab monotherapy market share is added to pembrolizumab + lenvatinib (i.e. it is assumed that patients who received IO monotherapy would get IO combination therapy if monotherapy was unavailable).
§ Pembrolizumab monotherapy is not available in UK practice for patients with pMMR disease – pembrolizumab monotherapy market share is proportionally redistributed across all other 2L therapies.
¶ Pembrolizumab monotherapy is not available in UK practice for patients with pMMR disease – pembrolizumab monotherapy market share is proportionally redistributed across all other 2L non-immunotherapy treatments.

Table 19. Subsequent treatments used in KEYNOTE-868 (NRG-GY018) adjusted for use in model: All comer

pMMR	**Pembrolizumab + CT (IO redistributed)**	**CT**			
		Unadjusted	**(a) IO combined**	**(b) IO mono redistributed**	**(c) IO mono redistributed to non-IO**
Carboplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin + paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dostarlimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Doxorubicin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Letrozole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Megestrol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + lenvatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No active treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% of 2L-treated patients who get IO	-	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 2L, second line; CT, carboplatin + paclitaxel; IO, immunotherapy.
Calculated from dMMR to pMMR treatment mix sets based on ratio of dMMR to pMMR amongst patients who had subsequent therapy in each treatment arm.

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4 Additional insights from clinical experts

To inform the DG consultation process, MSD collected insights from 11 clinical experts. All experts were consultant clinical or medical oncologists who treat patients with endometrial cancer in their practices across the UK. Insights were gathered via 1:1 calls between each expert and MSD.

Questions (1) and (2) relate to subsequent immunotherapy use after first-line CT. The responses collected from each expert are summarised in Table 20.

Question (3) relates to long-term resource use in the progression-free health state. The responses collected from each expert are summarised in Table 21.

1. **Amongst patients with primary advanced/recurrent endometrial cancer who progress on first-line (1L) treatment with carboplatin + paclitaxel:**
   a. What proportion of progressive dMMR patients receive active† second-line (2L) treatment?
   b. What proportion of progressive pMMR patients receive active† second-line (2L) treatment?

2. **Amongst patients receiving active† second-line (2L) treatment following progression on first-line treatment with carboplatin + paclitaxel**:
   a. What proportion of dMMR patients receive immunotherapy?
   b. What proportion of pMMR patients receive immunotherapy?

   († 'Active' treatment refers to disease-modifying treatment, which could include: Immunotherapy, chemotherapy, hormone therapy, or radiotherapy. Purely palliative treatment would not be considered 'active'.)

3. **For a patient with primary advanced/recurrent endometrial cancer who has completed first-line standard of care treatment and who remains progression-free:**
   a. What is the interval/frequency of the following regular monitoring activities, excluding ad hoc adverse event management?
      i. Blood tests
      ii. CT scans
      iii. Outpatient clinic visits (i.e. consultations with an oncologist or nurse specialist)
   b. Is there a timepoint at which a patient who remains progression-free would stop having these regular monitoring activities? Please give your answer in months or years from the point of first-line treatment initiation.

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Table 20. Clinical expert opinion relating to subsequent immunotherapy use after 1L CT

Clinical expert	dMMR			pMMR		
	(1a) % of patients who get 2L treatment	(2a) % of 2L-treated patients who get IO	% of patients who progress who get 2L IO†	(1b) % of patients who get 2L treatment	(2b) % of 2L-treated patients who get IO	% of patients who progress who get 2L IO†
A	60%	All (100%)	**60%**	60%	60%	**36%**
B	80-90%	75%	**60–67.5%**	50-60%	60%	**30–36%**
C	70%	90%	**63%**	70%	85%	**59.5%**
D	90%	90-100%	**81–90%**	90%	80-90%	**72–81%**
E	70%	70–85%	**49–59.5%**	60–65%	50–55%	**30–35.75%**
F	80%	50%	**40%**	80%	20%	**16%**
G	80%	80%	**64%**	80%	50–60%	**40–48%**
H	75–80%	80%	**60–64%**	75–80%	70–80%	**52.5–64%**
I	65%	80%	**52%**	65%	50%	**32.5%**
J	95%	80-90%	**76–85.5%**	95%	75%	**71.25%**
K	>90%	85–90%	**76.5–81%**	>90%	85–90%	**76.5–81%**
Average	***77.7–79.1%***	***80–83.6%***	***62.0–66.0%***	***74.1–75.9%***	***62.3–65.9%***	***46.9–51.0%***
Average (ex. F) ‡	***77.5–79.0%***	***83.0–87.0%***	***64.2–68.7%***	***73.5–75.5%***	***66.5–70.5%***	***50.0–54.5%***

† Calculated by multiplying expert responses to questions (1) and (2).
‡ Estimates from expert F relating to the proportion of 2L-treated patients who get IO (Q2) were markedly lower than from all other experts for both dMMR and pMMR, therefore these estimates were removed from the overall assessment to prevent skewing the average results.

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Table 21. Clinical expert opinion relating to regular monitoring activities in the PF state

Clinical expert	(3a) Frequency of regular monitoring activities in the PF state			(3b) Duration of regular monitoring activities in the PF state
	Bloods	Scans	Visits	
A	6 weeks 1 yr post-IO: 6 months	6 weeks 1 yr post-IO: 6 months	8-12 weeks	Would not discharge
B	Patients with PR: 3 months Patients with CR: 1yr: 3 months 2-5yr: 4-6 months	Patients with PR: 3 months Patients with CR: 1yr: 3months 2-5yr: 4-6 months	Patients with PR: 3 months Patients with CR: 1yr: 3months 2-5yr: 4-6 months	May discharge at 5 yrs patients who had a CR
C	1-2yrs: 6 months 3-5yrs: 12 months	1-2yrs: 6 months 3-5yrs: 12 months	3-4 months 3-5yrs: 6 months	May discharge at 5 yrs if disease-free
D	1-2yrs: 3 months 3-5yrs: 6 months 6-10yrs: 12 months	Driven by symptoms & stage at diagnosis.	1-2yrs: 3 months 3-5yrs: 6 months 6-10yrs: 12 months	Not stated
E	1-2yrs: 3 months	1-2yrs: 2-3 months 3yrs+: 4 months 4yrs+: 6 months	1-2yrs: 3 months	Not stated
F	1-2yrs: 3 months 3-5yrs: 6 months	Patients with CR: none Patients with PR: 3 months	1-2yrs: 3 months 3-5yrs: 6 months	May discharge at 5 yrs patients who had a CR
G	1yr: 3 months 2-3yrs: 6 months 4yrs+: 12 months	1yr: 3 months 2-3yrs: 6 months 4yrs+: 12 months	1yr: 3 months 2-3yrs: 6 months 4yrs+: 12 months	Would not discharge
H	1-2yrs: 3 months 3-5yrs: 6 months 6yrs+: 12 months	1-2yrs: 3 months 3-5yrs: 6 months 6yrs+: 12 months	1-2yrs: 3 months 3-5yrs: 6 months 6yrs+: 12 months	May stop scans for some patients after 5 yrs, but not discharged
I	1yr: 3 months 2yrs: 4 months	1yr: 3 months 2yrs: 4 months	1yr: 3 months 2yrs: 4 months	May stop at 5 yrs if no measurable disease
J	1-2yrs: 3 months 3-5yrs: 6 months	1-2yrs: 3 months 3-5yrs: 6 months	1-2yrs: 3 months 3-5yrs: 6 months 6yrs+: 6-12 months	Stop scans at 5 yrs but not discharged.
K	First few yrs: 3 months Few yrs+: 6 months	First few yrs: 3 months Few yrs+: 6 months	First few yrs: 3 months Few yrs+: 6 months	May discharge after 3 yrs if PF

Abbreviations: CR, complete response; IO, immunotherapy; PF, progression-free; PR, partial response; yrs, years.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Gemma EMINOWICZ

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	NONE
Name of commentator person completing form:	Gemma EMINOWICZ

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	I think this draft summarises the evidence reasonably and has interpreted the data fairly
2	My only question is whether there is a way to separate the mismatch repair deficient and proficient population in view of the differential response seen in these cohorts.
3	I do not dispute the outcome
4	
5	

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6	

Insert extra rows as needed

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External Assessment Group's report for pembrolizumab with platinum-based chemotherapy then pembrolizumab maintenance for treating advanced or recurrent endometrial cancer ID6381

Produced by	*Warwick Evidence/Birmingham Centre for Evidence and Implementation Science*
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Declared competing interests of the authors
None

Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

Please note that: Sections highlighted in [redacted]. Figures that are CIC have been bordered with blue. [redacted] is highlighted in pink.

1 Committee draft recommendations and consultation responses

This section summarises elements of the Committee draft recommendation together with responses from one or more consultees:

- the company Merck Sharp & Dohme (UK) Ltd (MSD)

Where relevant these are followed by an EAG response.

1.1 Section 1: Recommendations

Committee: Pembrolizumab with carboplatin and paclitaxel should not be used for untreated primary advanced or recurrent endometrial cancer in adults.

1.2 Section 3.3: Mismatch repair

Committee: Endometrial cancer can be mismatch repair deficient (dMMR; around 25% to 30% of cases) or proficient (pMMR; around 70% to 75% of cases). dMMR endometrial cancer has a better prognosis and response to treatment than pMMR endometrial cancer.

1.3 Section 3.3: Clinical management

Committee: Current treatments are not curative, if endometrial cancer returns after chemotherapy treatment, the subsequent treatment options can also cause significant side effects. There is an unmet need for more effective treatments for people with untreated advanced or recurrent endometrial cancer.

1.4 Section 3.4: Efficacy of pembrolizumab + CT in KEYNOTE-868 (NRG-GY018)

EAG summary: The committee found that pembrolizumab plus chemotherapy significantly improves progression-free survival (PFS) in advanced or recurrent endometrial cancer, but overall survival (OS) benefits were not statistically significant—possibly due to short follow-up. They agreed treatment could be stopped after two years, and that the results are applicable to NHS practice. The company (MSD) emphasized the trial showed clear PFS benefits and, while not powered for OS, trends suggested improved survival. In the overall population, OS data favoured pembrolizumab, with confidence intervals indicating a potential benefit.

EAG critique: The EAG does not agree with the company's assertion that non-significant OS results 'should not be interpreted as evidence that pembrolizumab + CT does not improve OS' as this statement risks overstating the strength of the evidence.

The EAG also note that in a trial that was not powered to detect OS differences across MMR subgroups, observed trends should be considered exploratory and hypothesis-generating rather than confirmatory.

Lastly, the company does not address the committees concern regarding limited data follow-up and potential immaturity of the current survival estimates. The EAG proposes exploring options such as a data collection agreement via Cancer Drugs Fund, modelled OS projections or offering more timelines for additional mature data to resolve uncertainty

1.5 Section 3.5: Modelling of MMR subgroups

EAG Summary: The company agreed with the EAG on OS modelling for the dMMR subgroup and maintained different preferences for PFS modelling due to perceived alignment with clinical expectations of an early and flatter plateau, and slightly better long-term plausibility. For the pMMR subgroup, the company strongly disagreed with the EAG's choices, particularly for PFS, arguing their models better reflected expert opinion and captured the potential for long-term benefit better.

While the EAG recognises that any differences in extrapolated outcomes can lead to divergence in the ICERs, it is important to stress that the survival modelling should be data-driven via an integrated assessment of statistical goodness-of-fit, plausibility of long-term hazards, visual fit to the observed Kaplan-Meier data, and, where appropriate, relevant clinical expert input.

Due to the timing constraints and the post-AC nature of the work, clinical engagement for the survival analysis of MMR subgroups was limited. Nevertheless, the EAG maintains that the chosen models reflect a cautious, methodologically grounded approach that balances model fit with long-term plausibility, avoiding overreliance on extrapolations unsupported by trial data maturity. It was also explicitly stated in the EAG's document post-AC1 that piecewise models were not considered due to these time constraints.

EAG critique:

dMMR subgroup

The EAG's modelling for the dMMR subgroup aimed to balance clinical expectations with statistical validity and model plausibility. While expert opinion informed model selection, preference was given to standard parametric models that offered interpretable extrapolations and avoided overfitting. The use of spline-based extrapolations, though explored, was not preferred due to their structural complexity and optimistic bias respectively. The EAG's base case represents a cautious and methodologically sound approach considering the immaturity of the trial data. Piece-wise models were not considered due to time-constraints.

PFS: Pembrolizumab + CT

According to the company, both the company's and EAG's models were judged plausible by expert reviewers, with the company preferring the generalised gamma model and the EAG selecting the log-logistic model. The EAG explored a range of standard parametric and spline-based approaches. While spline models, such as the 2-knot normal model, offered a superior visual fit to the observed KM data and hazards plot, they were ultimately not used in the base case due to concerns around overall optimistic long-term projections, particularly in the context of limited follow-up data.

The EAG therefore selected the log-logistic model as a compromise, providing reasonable fit to the observed data while yielding more conservative extrapolations than spline models. Although the company argues that the generalised gamma model better reflects clinical expectations of a plateau in long-term PFS, the EAG found the hazard shape of the log-logistic to be more appropriate and aligned with observed data maturity.

Notably, the difference in extrapolated estimates between the EAG's preferred log-logistic model and the company's generalised gamma models are relatively small, and both fall within a plausible range. The EAG acknowledges that all standard parametric models—including the log-logistic and generalised gamma—tend to be pessimistic in immunotherapy settings, but this reflects a cautious stance in the absence of mature long-term data. This approach to survival modelling errs on the side of caution pending confirmatory data in the long-term.

PFS: CT only

The company preferred the two-piece gamma model, citing visual fit and expert input, while the EAG preferred the generalised gamma model, which offered a reasonable fit to the trial data while maintain a more parsimonious parametric structure.

While the company's two-piece approach may better capture the short-term, particularly within the trial observation period, the EAG judged that it introduced additional model complexity without sufficient justification given the relatively limited differences in fit. Furthermore, given the immaturity of the PFS data and the uncertainty around the post-trial trajectory, the generalised gamma model provided a more stable and interpretable long-term extrapolation.

Spline models were also considered, and while these provided improved fit to the observed data and hazard functions, they projected unrealistically optimistic PFS over the long-term, thus were not considered.

OS: both arms

The EAG and company are aligned in their OS extrapolations for both arms, preferring the exponential model for the CT only arm, and the log-logistic model for the pembrolizumab + CT arm.

pMMR

The EAG's modelling choices in the pMMR subgroup reflects a methodologically cautious approach to handling immature survival data. While the company strongly favours curves that reflect long-term benefit, particularly for the pembrolizumab + CT arm, these often rely heavily on assumptions rather than the empirical evidence observed in KEYNOTE-868. The EAG's base case used spline models in this subgroup since they demonstrated clear improvement in fit and plausibility, while also exploring a broad range of alternative forms in sensitivity analyses. The use of 1- and 2-knot splines was guided by empirical fit rather than theoretical preference.

While clinical input is valuable, the EAG has limited access to such advise post-AC1 due to practical constraints. Nevertheless, the modelling is grounded in strong statistical principles and represents a transparent and justifiable extrapolation of the available, observed data.

PFS: Pembrolizumab + CT

The company asserts that the EAG base case (1-knot hazard spline) had poor visual fit and results in implausible PFS hazard ratio dynamics, including crossing the CT PFS curve at 5.5 years. However, the EAG assessed a wide range of spline-based models, including 2-knot spline models which, indeed, were found to provide the best overall fit. While the 1-knot spline was selected for parsimony and easier interpretability, and had good visual fit, the EAG agrees that the 2-knot models offer slightly better tail fit and were included in sensitivity analyses.

Importantly, the apparent curve crossing highlighted by the company is an artefact of highly uncertain long-term projections and does not undermine the validity of the model within the observed trial time horizon, which is more in line with data-driven analysis rather than calibrating models to expert opinion. Considering data immaturity and ongoing treatment effect uncertainty, a cautious approach to extrapolation is warranted.

Again, it should be noted that the EAG were unable to explore piecewise models due to a lack of time, therefore the choice of model was based on either parametric models or splines, with the 1-knot spline model chosen due to parsimony, good visual fit, and providing similar estimates to the 2-knot models.

PFS: CT only

The company criticised the EAG's PFS curve (2-knot hazards) for being overly optimistic, citing expert input that 2-3% would be more realistic. However, the EAG selected this curve as its base case due to its strong visual fit and reasonable hazard function. Other 2-knot spline models were explored and produced similar results, while the 1-knot models, such as the company's chosen 1-knot odds spline model, had worse visual and hazards fit.

While the company's landmark estimates are noted, it is based on advisory board input rather than empirical data, and long-term PFS assumptions remain speculative at best. On the other hand, the 2-knot spline models offer superior fit to observed data and more credible hazard trajectories.

OS: Pembrolizumab + CT

The company argues that the EAG's base case (1-knot normal spline) is pessimistic and fails to reflect the potential for long-term responders, referencing a 14% complete response rate in KEYNOTE-868, While the log-logistic was judged plausible, the EAG selected the 1-knot spline due to superior fit to the observed KM data and stable hazard behaviour.

While the CR rate does suggest that a proportion of patients may experience durable benefit, this should not be conflated with evidence for a long tail in OS in the absence of long-term follow-up. The company's log-logistic model implies a flatter hazard than observed in the trial and may overstate survival benefit in later years.

While the EAG acknowledges the challenges of modelling OS with still-maturing data, the spline approach captures short to mid-term patterns while avoiding overly optimistic long-term extrapolation, which would require stronger empirical justification and not relying exclusively on advisory boards and expert opinions.

OS: CT only

The company notes that differences in long term extrapolation between their chosen model (gamma) and the EAG's chosen model (1-knot hazard) are similar. The EAG justified the choice of the 1-knot hazards spline model in the document post-AC1, stating better visual and hazards fit, but acknowledges that the gamma and other parametric models were reasonable.

Given the similarity in outputs, this modelling choice does not appear to be a key driver of differences in cost-effectiveness analyses and both distributions were included in scenario analyses. Clinical input may support gamma as a plausible option, but the spline model was retained in the EAG base case for consistency across outcomes and its stable hazard function.

1.6 Section 3.8: Starting age in the economic model

EAG summary: In the original appraisal, the EAG was concerned that the starting age in the economic model was too low (as advised by EAG's clinical expert and review of external literature sources). The EAG preferred to use a starting age of **67.1** years, which was the starting age in NICE's technology appraisal on dostarlimab with platinum-based chemotherapy for treating advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency

(TA663).[1] Post-AC1, the EAG updated the starting ages in its base case to the company's chosen values as they more closely aligned with data received from the CDF lead. Following DG comments, the company updated the starting age for the dMMR population from **65.7** years to **65.4** years, i.e., mean age of all patients who have been treated with dostarlimab + CT for dMMR endometrial cancer previously untreated in the advanced/metastatic setting in the UK NHS. The company maintains the starting age for pMMR the same as in its original submission as no data was available for pMMR patients from CDF data received which aligned with the population considered in this appraisal.

EAG critique: The EAG accepts the company's new approach and applies the same starting ages as the company in the revised EAG base case.

1.7 Section 3.9: Health state utilities values used in the model

EAG summary: Regarding utility values, in the original appraisal the EAG and committee were concerned about the use of utility values from a population of dMMR patients, to be used for both dMMR and pMMR subgroup modelling.

Previously, the company used utility values from KEYNOTE-158 since no utility data was collected in KEYNOTE-868. Other quality of life outcomes were collected in KEYNOTE-868, however these were only collected for the pMMR population, preventing any comparison being made. KEYNOTE 158 was a single arm study which only included people with dMMR disease, again meaning no comparison was possible.

The company's comments on the draft guidance related to utility values revolve around two key points. Firstly, that the utility information is generalisable across the dMMR and pMMR subgroups. Secondly, that the company's new source of utility value for the progression-free subgroup is an improvement over the previous source.

EAG critique:

Utility Values Across dMMR and pMMR Subgroups

To support the generalisability assumption, the company state that the main differences between the health states are likely to be captured in the subgroup modelling due to the differences in PFS and OS outcomes. The EAG accepts that

this is likely the main driver of the difference in cost-effectiveness outcomes between the subgroups, however maintains that the impact of subgroup-specific utilities should still be explored.

The company then highlights how the response rate in KEYNOTE-868 is higher than in KEYNOTE-158. They claim that this means the utility values are likely to be conservative. The EAG does not consider that these response rates clearly support this conclusion, not least because of the correlation between health states and response status.

The company present an analysis comparing quality-of-life outcomes from KEYNOTE-775, a phase III trial of pembrolizumab plus lenvatinib for advanced endometrial cancer, which shows broadly similar outcomes between the whole population and the pMMR population.

The EAG considers the analysis limited for two reasons. Firstly, rather than compare dMMR to pMMR, the company compares the pMMR subgroup to all-comers. Given that pMMR makes up 84% of the population, it is no surprise that there is minimal difference observed. Secondly, the analysis is not broken down into health states, so any differences within a health state may be countered by differing health state occupancy.

The company cite two further studies (RUBY and KEYNOTE-B21) reporting they show similar utility values across dMMR and pMMR subgroups. The analysis of KEYNOTE-B21 is limited by the fact that the only reliable comparison is for an earlier stage in the treatment pathway than the desired population, whilst the RUBY trial is limited by the fact it is a phase III trial investigating dostarlimab+CP for advanced and recurrent endometrial cancer, rather than pembrolizumab. However both suggest a small, potentially negligible, difference between the subgroups, though no formal hypothesis testing for a difference was presented. (RUBY: 0.794 vs 0.776 for progression-free, 0.734 vs 0.724 for post-progression).

Finally the company states that concerns about the progression-free utility value from KEYNOTE-158 being too high for the pMMR population, owing to the overrepresentation of people with better responses from the dMMR subgroup, is not a major concern as the benefits in this health-state over the model time-horizon will largely be accrued by the people with a good response within the pMMR subgroup.

Whilst the EAG considers this plausible, there is not enough data to support this conclusion.

In summary, the company has not explored implementing subgroup-specific utility values. The lack of EQ-5D collection from KEYNOTE-868 remains a missed opportunity, and remains a point of uncertainty. However, across the comparisons presented by the company, utility values for the pMMR subgroup seem consistently slightly higher than the dMMR subgroup, supporting the company's suggestion that it is conservative to use dMMR utility values when modelling the pMMR population. Any differences in utility values are likely to be small and have little impact on the cost-effectiveness modelling.

New company preferred utility values

Despite defending the use of KEYNOTE-158 utility values earlier in its response, the company switches to use a pre-progression utility value from KEYNOTE-B21, whilst maintaining the use of a post-progression utility value from KEYNOTE-158. This change was not requested by EAG or committee.

The population of KEYNOTE-B21 features patients at an earlier stage in the treatment pathway, and so the company takes the utility value for the post-disease recurrence population, considering that this overlaps with the starting population of KEYNOTE-868. Due to the results for the dMMR lacking face validity (i.e. [redacted]) the company use only the value for the pMMR population ([redacted]), but use for all analyses (both subgroups and pooled). The EAG are concerned that the lacking face validity may question the reliability of the pMMR values.

The EAG accepts there is some overlap of the post-disease recurrence population of KEYNOTE-B21 and starting population of KEYNOTE-868, but does not consider these populations identical.

Firstly, there are likely to be differences in the previous therapies received, and there are likely differences in the treatment they are receiving whilst in this health state. Furthermore, the EAG's clinical expert supported maintaining the use of utility values from KEYNOTE-158 due to greater similarity in the populations. The EAG prefer not to mix sources of utility values unless there is good justification for doing so. The company's analysis also has one value coming from a pMMR population, and the

other from a dMMR population. In summary the EAG does not consider the company's revised utility values to be an improvement, despite coming from a larger sample size (relevant sample size from KEYNOTE-158 [redacted]). Hence the EAG maintains the use of utility values in the original appraisal, however using the company's newly preferred utility values has a small impact on the ICER.

1.8 Section 3.10: Treatment effect waning

EAG summary:

In the original all-comer population submission, both the company and EAG assumed no treatment waning in their base case but explored several scenarios where waning was applied to the OS curve for patients who did not achieve an objective response (24.8% in the pembrolizumab+CT arm). The committee noted that applying treatment waning resulted in a small change in the quality-adjusted life years (QALYs) and requested the exploration of a scenario in the dMMR and pMMR subgroups where treatment waning applies to all patients, regardless of response status. The company has provided further justification for not applying treatment waning and explored two additional scenarios: one whereby TEW is applied to all patients who did not achieve a complete response and another scenario where waning applies to all patients regardless of treatment response. The EAG notes that it is important to consider that treatment waning refers to relative efficacy between the arms in terms of hazard rates, and not an absolute loss of effect of pembrolizumab.

EAG critique:

The company cites several reasons for not incorporating treatment waning in the economic modelling including the mechanism of action of immunotherapies, long-term data from trials showing some duration of effect after stopping Pembrolizumab, trial data from KEYNOTE-868, implicit treatment effect waning in some survival curves and precedent in previous technology appraisals in EC.

Mechanism of action

The first justification relates to the mechanism of action of immunotherapies. Immunotherapies activate the body's immune system to recognise and target cancer cells during therapy and, in some cases, long after treatment stops leading to durable response and sustained treatment benefit. The company cites data from KEYNOTE-868, showing that patients who received pembrolizumab+CT had a higher response rate than those who received CT alone (pMMR: 72.3% vs 59.0%; dMMR: 82.1% vs 71.6%, respectively) and a longer duration of response. The EAG believes it is plausible that the treatment effect continues for some time after stopping treatment, however, clinical advice to the EAG in TA779 suggested that patients who did not achieve a complete response may lose their response after stopping treatment, indicating that treatment effect wanes over time.[2] The CDF for TA737 stated that "*it is very likely there will be long-term survivors but there will also be people who relapse after 2 years and stated that although it is unclear if there is a treatment waning effect, it is a reasonable assumption*".[3] Furthermore, given that pembrolizumab is subject to a 2-year stopping rule, the DOR KM curves presented by the company showing a plateau between years 1-2 do not demonstrate whether the treatment effect is sustained beyond that timepoint and is insufficient evidence to suggest treatment waning does not take place at all.

The EAG considers this point may have little relevance to the waning of relative treatment effect, as the company fail to consider that immunotherapies are routinely available as a subsequent treatment in the comparator arm, and it is unclear why the long-term hazard rates would not be similar (i.e. when the pembrolizumab arm has stopped receiving immunotherapy, but those randomised to SOC and remaining alive are receiving immunotherapy).

Long-term data from trials showing some duration of effect after stopping pembrolizumab

Another reason for not applying treatment waning relates to insufficient evidence from trials to substantiate whether waning occurs in immunotherapies. The company argues that there is long-term data showing sustained treatment benefit following discontinuation from pembrolizumab, citing several trials including KEYNOTE-158

(pembrolizumab monotherapy for patients with previously treated dMMR tumours), KEYNOTE-006 (pembrolizumab, for advanced melanoma) and KEYNOTE-024 (pembrolizumab monotherapy in PD-L1 ≥50% NSCLC).

The most promising data comes from KEYNOTE-006, which reported OS HRs of 78.1%, 58.7% and 21.8% for complete responders, partial responders and non-responders and an overall 10-year OS HR of 0.71. However, without information on the number of patients at risk in the latter years, these results must be interpreted with caution. Furthermore, the EAG considers it unlikely that the sustained treatment benefit observed in advanced melanoma patients will also be seen by patients with advanced and recurrent endometrial cancer due to differences in patient characteristics, disease mechanisms and treatment efficacy. Clinical expert advice to the committee for TA661 states that "treatment effect duration for pembrolizumab could not be transferred from one disease area to another because of differences in the physiology and genetic profile of the tumours".[4]

The longest follow-up data for patients with dMMR endometrial cancer treated with pembrolizumab monotherapy comes from KEYNOTE-158. The company states that of the 42 patients who had a response in the EC subgroup, [redacted] were still in response at 3, 4 and 5 years respectively. The EAG accepts that there is some evidence to support sustained treatment benefit after discontinuing treatment however, the duration of effect is uncertain due to small number of patients at risk. In addition, it is unclear whether the duration of this effect can be generalised to patients with pMMR EC, given the lower response rate and prognosis observed in this subgroup (CR of 14.3% vs 31.6% in pMMR and dMMR respectively, KEYNOTE-868). Most importantly, a single arm study is unable to inform on relative efficacy, which is the point of consideration here.

Data from KEYNOTE-868 supports sustained treatment benefit

A further argument provided by the company is that there is not enough evidence from KEYNOTE-868 to indicate treatment waning because the KM curves for OS and PFS began to separate early in the trial and remained separated during follow-up. The company also presented time redependent HR plots, showing the HR fluctuates over the trial period but remains below 1, suggesting that the long-term

benefits of pembrolizumab treatment are stable or continuing to diverge in all 3 cohorts. The EAG notes that the data from KEYNOTE-868 is immature due to few patients remaining at risk at 36 months who received pembrolizumab ([redacted]). Thus, it is highly uncertain how long the benefits of pembrolizumab are retained after stopping treatment.

The EAG is concerned that citing a lack of observed waning to justify not applying any form of waning effect discourages companies from collecting long-term follow-up, and instead submitting short-term follow-up, which sets an undesirable precedent from the position of the tax-payer.

Figure 1: Overall survival hazard rates from company dMMR base case

Figure 2: Overall survival hazard rates from company pMMR base case

Treatment effect waning is modelled implicitly in some independently fitted survival curves

Citing Taylor et al., the company explains that some independently fitted survival models explored in scenario analyses predict converging hazards, implying that treatment waning is already accounted for and any additional waning applied after a specified timepoint would result in double counting of the effect. The company acknowledges that such convergence is not observed in the base case hazard plots for either subgroup, except in the scenario analyses where log-logistic and 2-knot odds curves were selected for the CT arm in the dMMR and pMMR subgroups respectively. It is unclear to the EAG why this commentary is necessary, as it simply highlights that treatment waning is not implicitly modelled in the base case. In the scenarios where there was convergence in the hazard plots, the company's base case ICER increased by 25% and 28% in the dMMR and pMMR subgroups, highlighting that treatment waning remains an important driver of uncertainty the economic model.[5]

Precedent in immunotherapy appraisals in endometrial cancer

Finally, the company argues against modelling treatment waning because they believe it is considered a highly conservative approach based on clinical evidence and precedent in previous immunotherapy appraisals for endometrial cancer. The EAG accepts that although treatment waning may be considered a conservative assumption because long-term trial data shows treatment response is sustained in certain types of cancer, there is a broad consensus amongst committees that assuming a gradual treatment waning effect, usually between 5-7 years and 7-9 years after starting treatment in endometrial cancer and 3-5 years in other cancers, is a reasonable assumption for immunotherapy appraisals.[3, 5-9] In TA779, the committee preferred the EAG's assumption of immediate treatment waning following discontinuation, given data immaturity and suggests that long-term trial data could help mitigate some of the uncertainty.

Clinical advice to the EAG, although conflicting, aligns with the treatment waning assumptions preferred by committees on previous pembrolizumab appraisals. One

expert expects a complete loss in treatment benefit after 5 years from the start of treatment given that OS curves for patients treated with pembrolizumab monotherapy and pembrolizumab+CT merge with the OS curve for patients receiving CT roughly around 5 years in several trials with longer follow-up involving multiple cancer types.[10, 11] The second expert has a more pessimistic view and believes that it is likely that the treatment effect would wane over a 2-year period after stopping treatment, with no effect by 5 years. These views are consistent with the large proportion of responders who only achieved partial response (Table 1), and whose response is more likely to be linked to receiving ongoing treatment.

Table 1: Response outcomes from pembrolizumab arm of KEYNOTE-868

	All-comers
Total Responders	240/319 (75.2%)
Partial Responders	178/240 (74.2%)
Complete Responders	62/240 (25.8%)

In conclusion, the EAG agrees that is clinically plausible for patients to continue benefiting from pembrolizumab even after stopping treatment, however, due to the pivotal trial's limited follow-up, the duration of effect is highly uncertain and there is insufficient evidence to conclude that treatment waning does not occur over time. Based on the rationale provided by the company, further clarification from the EAG's clinical advisors and precedent set in EC appraisals, the EAG considers it appropriate to include gradual treatment waning applied to all patients between years 5-7 after starting treatment, in line with TA904 and TA737, representing a compromise between the clinical advice received and previous appraisals. Due to the uncertainty around the true long-term relative efficacy, this assumption could still be overestimating the benefit of pembrolizumab. Clinical advice and guidance from the literature on applying effect waning, suggests that gradual waning is a more appropriate than immediate waning because patients are not expected to lose all relative benefit after a specified time point.[12] For completeness, we have explored both EAG clinical expert assumptions in scenario analyses.

Figure 3: Hazard rates for EAG analyses exploring waning

1.9 Section 3.11: Resource use estimates in the economic model

EAG summary: In its original report, the EAG noted that the resource use estimates applied by the company in its base case likely underestimated resource use for the pembrolizumab + CT arm. This followed the EAG clinical expert's opinion on the level of resource us likely to be observed clinically for patient population under consideration. In the DG, the experts showed preference for the estimates provided by the EAG experts while on treatment as this conforms to the dosing regimen for chemotherapy every 3 weeks initially, and maintenance with pembrolizumab every 6 weeks from week 18. Following the CDF clinical lead's advice that pembrolizumab will sometimes be administered 3-weekly instead of 6-weekly, the committee

concluded that even the EAG expert's estimates may still underestimate the resources used by the pembrolizumab +CT arm while on treatment.

To respond, the company obtained further clinical experts' opinions on level of resource use for patients who remain progression free. The updated economic model's base case values, according to the company's DG response, reflect insights gained from the exercise and a review of prior advisory board and EAG expert estimates (Table 2). Additional scenarios explored 3-weekly pembrolizumab maintenance dosing which was the committee's preference. However, the company noted that the SmPC specifies a 200mg dose of KEYTRUDA (pembrolizumab) every 3 weeks for 6 cycles with chemotherapy, then 400mg every 6 weeks for first-line treatment of advanced or recurrent EC. This dosage regimen differs from other pembrolizumab indications, where the SmPC does not specify the dosing schedule.

Table 2: **Corrected resource use in the updated economic model**

Health state	Resource	Frequency	Frequency per week (applied in model)	Source
Pembrolizumab + CT				
PFS (On treatment):	Computed tomography scan	12 wks (3 mo)	0.08	MSD advisory board; EAG clinical expert
	Outpatient visit	*Cycle 0-17*: 3 wks	0.33	
	Blood test	*Cycle 18-104*: 6 wks	0.17	
PFS (Off treatment): pembrolizumab + CT	Computed tomography scan	*Cycle 0-104*: 12 wks (3 mo)	0.08	MSD advisory board; EAG clinical expert; MSD clinical expert insights
	Outpatient visit	*Cycle 105+:* 26 wks (6 mo	0.04	
	Blood test			
CT				
PFS (On treatment): CT	Computed tomography scan	12 wks (3 mo)	0.08	MSD advisory board; EAG clinical expert
	Outpatient visit	*Cycle 0-17*: 3 wks	0.33	
	Blood test			
PFS (Off treatment): CT	Computed tomography scan	*Cycle 0-104*: 12 wks (3 mo)	0.08	MSD advisory board; EAG clinical expert
	Outpatient visit	*Cycle 105+:* 26 wks (6 mo)	0.04	
	Blood test			
Source: Table 7, Decision Guidance MSD Response				

EAG critique: The EAG's clinical experts considered the updated resource use estimates acceptable and likely reflective of clinical practice. The EAG thus applies the company's new estimates in its revised base case.

1.10 Section 3.12: Subsequent treatment mix

EAG summary:

In its original report, the EAG explored the appropriateness of the subsequent treatment mix approach applied by the company in its base case in the all-comer population. The main differences noted by the EAG was that advice from their clinical experts was that standard second-line treatment for patients who received carboplatin and paclitaxel at first line was pembrolizumab + Lenvatinib not pembrolizumab monotherapy. The EAG explored scenario whereby the pembrolizumab monotherapy was replaced by pembrolizumab +CT at second-line. This was further reiterated at the committee meeting by the clinical experts who explained that pembrolizumab with Lenvatinib is available for second treatment of dMMR and pMMR cancer, but pembrolizumab monotherapy is available for only people with dMMR cancer as second-line treatment. It was mentioned that because of the toxicity associated with Lenvatinib, most dMMR cancer patients would receive pembrolizumab monotherapy. Also, almost all pMMR patients who had chemotherapy at first line will receive pembrolizumab + Lenvatinib as second line. But the dose of Lenvatinib is reduced, with some patients completely stopping Lenvatinib because of its associated toxicity. Further insights were given by the Cancer Drugs Fund (CDF) clinical lead who stated that almost all dMMR patients now receive Dostarlimab (an immunotherapy) as first line and so will not be rechallenged by pembrolizumab monotherapy or pembrolizumab combination with Lenvatinib (another IO). But this cannot be considered in this appraisal because Dostarlimab is currently funded by CDF. Consequently, the company re-visited their previous subsequent treatment mix assumptions based on MMR status as advised by the committee. The company states that the revised assumptions are based on consultation with 11 clinical experts from across the UK to understand the real-world use of IO after disease progression for EC patients who received first line carboplatin

+ paclitaxel. Table 3 shows the new set of subsequent treatment shares used in the revised base case for the MMR cohorts.

Table 3: Subsequent treatment mix used in the updated base case model

	dMMR		pMMR	
	Pembrolizumab + CT	**CT**	**Pembrolizumab + CT**	**CT**
Carboplatin	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin + paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
Dostarlimab	[redacted]	[redacted]	[redacted]	[redacted]
Doxorubicin	[redacted]	[redacted]	[redacted]	[redacted]
Letrozole	[redacted]	[redacted]	[redacted]	[redacted]
Megestrol	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + lenvatinib	[redacted]	[redacted]	[redacted]	[redacted]
Radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]
No active treatment	[redacted]	[redacted]	[redacted]	[redacted]
Source: Table 1, Decision Guidance MSD response				

EAG critique: The EAG considers the evidence in Table 20, Appendix 4 of the MSD DG response and the share allocation method explained by the company in their DG response to be appropriate. This now aligns the updated subsequent treatment market shares with the committee's and EAG clinical expert's advice. For completeness, the EAG presents the initial subsequent shares for the all-comer population and the MMR cohorts presented by the company (Table 4).

Table 4: Subsequent treatment mix for the for the pMMR and dMMR subgoups (original company base case)

Subsequent treatment	**ALL-comer population**	**pMMR**	**dMMR**
Pembrolizumab +CT arm			
Carboplatin	[redacted]	[redacted]	[redacted]
Carboplatin + paclitaxel	[redacted]	[redacted]	[redacted]
Doxorubicin	[redacted]	[redacted]	[redacted]

Letrozole	[redacted]	[redacted]	[redacted]
Megestrol	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]
Pembrolizumab + Lenvatinib	[redacted]	[redacted]	[redacted]
Radiotherapy	[redacted]	[redacted]	[redacted]
No active treatment	[redacted]	[redacted]	[redacted]
CT arm			
Carboplatin	[redacted]	[redacted]	[redacted]
Carboplatin + paclitaxel	[redacted]	[redacted]	[redacted]
Doxorubicin	[redacted]	[redacted]	[redacted]
Letrozole	[redacted]	[redacted]	[redacted]
Megestrol	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]
Pembrolizumab + Lenvatinib	[redacted]	[redacted]	[redacted]
Radiotherapy	[redacted]	[redacted]	[redacted]
No active treatment	[redacted]	[redacted]	[redacted]
Source: initial CS economic model for MMR cohorts, subsequent treatment worksheet			

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1.11 Section 3.14: Company and EAG's cost-effectiveness results

The updated company base case deterministic cost-effectiveness results, reported separately for dMMR, pMMR cohorts and all-comer population are reported in tables 5 - 7. Probabilistic sensitivity analyses, based on 1,000 iterations are presented in Table 8-Table 10. The deterministic cost-effectiveness ICERs for dMMR, pMMR cohorts and the all-comer population are similar and range between [redacted]K/QALY.

Table 5. Base case deterministic cost-effectiveness results: dMMR

Technologies	Total costs, £	Total LYG	Total QALYs	Inc costs, £	Inc LYG	Inc QALYs	ICER (£/QALY)
Pembrolizumab + CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2.24	[redacted]
CT	[redacted]	5.01	[redacted]	-	-	-	-

Table 6. Base case deterministic cost-effectiveness results: pMMR

Technologies	Total costs, £	Total LYG	Total QALYs	Inc costs, £	Inc LYG	Inc QALYs	ICER (£/QALY)
Pembrolizumab + CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.21	[redacted]
CT	[redacted]	2.55	[redacted]	-	-	-	-

Table 7. Base case deterministic cost-effectiveness results: All comer

Technologies	Total costs, £	Total LYG	Total QALYs	Inc costs, £	Inc LYG	Inc QALYs	ICER (£/QALY)
Pembrolizumab + CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.39	[redacted]
CT	[redacted]	3.79	[redacted]	-	-	-	-

The mean probabilistic cost-effectiveness results for dMMR, pMMR and all-comer population in the company's analyses are consistent with the deterministic results reported above (Table 8-Table 10). At a willingness to pay (WTP) threshold of £30,000/QALY gained, the probability of cost-effectiveness for dMMR, pMMR and all-comer population were [redacted]%, [redacted]% and [redacted]% respectively. The probability of cost-effectiveness at a WTP threshold of £20,000/QALY for the dMMR, pMMR and all-comer populations were [redacted]%, [redacted]% and [redacted]% respectively.

Table 8. Mean probabilistic base case results: dMMR

Technologies	Total costs, £	Total LYG	Total QALYs	Inc costs, £	Inc LYG	Inc QALYs	ICER (£/QALY)
Pembrolizumab + CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2.06	[redacted]
CT	[redacted]	5.02	[redacted]	-	-	-	-

Table 9. Mean probabilistic base case results: pMMR

Technologies	Total costs, £	Total LYG	Total QALYs	Inc costs, £	Inc LYG	Inc QALYs	ICER (£/QALY)
Pembrolizumab + CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.16	[redacted]
CT	[redacted]	2.54	[redacted]	-	-	-	-

Table 10. Mean probabilistic base case results: All comer

Technologies	Total costs, £	Total LYG	Total QALYs	Inc costs, £	Inc LYG	Inc QALYs	ICER (£/QALY)
Pembrolizumab + CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.38	[redacted]
CT	[redacted]	3.76	[redacted]	-	-	-	-

EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

The EAG revised base case cost-effectiveness estimates are reported separately for dMMR, pMMR and all-comer population.

dMMR

The EAG's adjustments to the company's base case model are presented in Table 11, showing the individual effect of each change as well as the combined effect of all changes cumulatively for dMMR subgroup. Table 12 and Table 13 show the EAG's estimated deterministic and probabilistic ICERs respectively.

The EAG's deterministic ICER for the dMMR subgroup was [redacted]/QALY, representing a [redacted]% increase from the company's base case ICER. The most influential adjustment was treatment waning assumption. All other assumptions had minimal impact on the base case ICER.

Table 11. EAG preferred model assumptions (dMMR cohort)

Preferred assumption	ICER (£/QALY)	Section in current report	Impact on company base case
Company base case ICER	[redacted]		
EAG 01: Generalised gamma model for PFS extrapolation; CT only	[redacted]	1.5	[redacted]
EAG 02: Log-logistic model for PFS extrapolation; Pembrolizumab + CT	[redacted]	1.5	[redacted]
Treatment waning from 5-7 years for all patients.	[redacted]	1.8	[redacted]

Utilities: KN-158 PFS: [redacted] PD: [redacted]	[redacted]	1.7	[redacted]
EAG base case (All changes applied)	[redacted]		[redacted]

Table 12. EAG deterministic base case cost-effectiveness analysis (with PAS price used for pembrolizumab), dMMR

Technologies	Total Costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Incremental QALYs	ICER (£/QALY)
CT	[redacted]	5.01	[redacted]				
Pembrolizumab + CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.08	[redacted]

Table 13. EAG probabilistic base case cost-effectiveness analysis (with PAS price used for pembrolizumab), dMMR

Technologies	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
CT	[redacted]	5.01	[redacted]				
Pembrolizumab + CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.95	[redacted]

Figure 4 and Figure 5 show the cost-effectiveness acceptability curves and scatterplots for the dMMR subgroup in the EAG's base case. At a willingness to pay (WTP) threshold of £20,000/QALY and £30,00QALY gained, the probability of cost-effectiveness for dMMR was [redacted]% and [redacted]% respectively.

Figure 4: Cost-effectiveness acceptability curve, EAG base case, dMMR

Figure 5: Figure 5 Cost-effectiveness plane, EAG base case, dMMR

EAG exploratory analyses dMMR

The exploratory analyses undertaken by the EAG for dMMR subgroup are presented in Table 14 below.

Table 14: EAG exploratory analyses, dMMR

Parameter varied	Base case value	Scenario value	Rationale	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Percentage change in ICER
Company base case ICER				[redacted]	2.24	[redacted]	
Treatment waning in OS	No treatment waning assumed	**Scenario 1** Gradual waning 5 to 7 years after starting treatment for all patients (**EAG base case**)	Precedent in previous NICE EC appraisals where patients discontinue treatment with immunotherapy after two years	[redacted]	1.13	[redacted]	[redacted]
		Scenario 2 Complete loss of treatment effect 5 years after starting treatment for all patients	EAG clinical expert 1	[redacted]	0.99	[redacted]	[redacted]
		Scenario 3 Gradual waning 3-5 years after starting treatment for all patients	EAG clinical expert 2	[redacted]	0.84	[redacted]	[redacted]

Parameter varied	Base case value	Scenario value	Rationale	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Percentage change in ICER
		Scenario 4 Gradual waning 5 to 7 years after starting treatment for patients with non-CR (**EAG base case**)	Scenario 1 applied to non-CR responders	[redacted]	1.51	[redacted]	[redacted]
		Scenario 5 Complete loss of treatment effect 5 years after starting treatment for patients with non-CR	EAG clinical expert 1 preference applied to non-CR patients	[redacted]	1.41	[redacted]	[redacted]
		Scenario 6 Gradual waning 3-5 years after starting treatment for non-CR patients	EAG clinical expert 2 preference applied to non-CR patients	[redacted]	1.31	[redacted]	[redacted]
Resource use frequency per week of blood test and outpatient visits in the CT arm (cycle 0-17)	PFS (on treatment): Blood tests - 0.33, outpatient visits - 0.33	PFS (on treatment): Blood test – 0.29 (cycle 0 - 17)	To evaluate the impact of a lower resource use in the CT arm.	[redacted]	2.24	[redacted]	[redacted]

pMMR

The EAG's adjustments to the company's base case model are presented in Table 15, showing the individual effect of each change as well as the combined effect of all changes cumulatively for pMMR subgroup. Table 16 and Table 17 show the EAG's estimated deterministic and probabilistic ICERs respectively.

The deterministic ICER increased from [redacted] (Company's base case) to [redacted] (EAG's base case), representing a [redacted]% increase from the company's base case ICER. The most influential adjustment was treatment waning assumption, followed by choice of OS extrapolation in the pembrolizumab + CT arm.

Table 15. EAG preferred model assumptions: pMMR cohort

Preferred assumption	ICER (£/QALY)	Section in current report	Impact on company base case
Company base case ICER [redacted]			
EAG 01: OS extrapolation for Pembrolizumab + CT: 1-knot normal	[redacted]	1.5	[redacted]
EAG 02: OS extrapolation for CT: 1 knot hazards	[redacted]	1.5	[redacted]
EAG 03: PFS extrapolation Pembrolizumab + CT: 1- knot hazards	[redacted]	1.5	[redacted]
EAG 04: PFS extrapolation CT: 2-knot hazards	[redacted]	1.5	[redacted]
Treatment waning from 5-7 years for all patients.	[redacted]	1.8	[redacted]
Utilities: KN-158 PFS: [redacted] PD: [redacted]	[redacted]	1.7	[redacted]

EAG base case (All changes applied)	[redacted]		[redacted]

Table 16. Deterministic cost-effectiveness results: pMMR (EAG base case)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	INMB (£)
Pembrolizumab + CT	[redacted]	[redacted]	[redacted]	-	-	-	-	-
CT	[redacted]	2.61	[redacted]	[redacted]	[redacted]	0.46	[redacted]	[redacted]

Table 17. Probabilistic mean cost-effectiveness results: pMMR (EAG base case)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	INMB (£)
Pembrolizumab + CT	[redacted]	[redacted]	[redacted]	-	-	-	-	-
CT	[redacted]	2.69	[redacted]	[redacted]	[redacted]	0.42	[redacted]	[redacted]

Probabilistic sensitivity analysis was performed on the EAG base case using 1,000 iterations drawn from parametric assumptions in the adapted economic model for the pMMR subgroup. Incremental costs were [redacted] and incremental QALYs 0.42 resulting in an ICER of [redacted] (Table 17). At a £30,000 WTP threshold pembrolizumab +CT returned a negative iNMB (-[redacted]) and iNHB ([redacted]). The cost-effectiveness scatterplot indicates that most iterations lie in the North-East quadrant i.e., Pembrolizumab+CT is both more costly and more effective than CT (Figure 6). While majority of the iterations were in the North-East quadrant, about [redacted]% of the points were presented in the North-West quadrant depicting that for those cost and effect pairs, the intervention was more costly and less effective. The cost-effectiveness acceptability curve (CEAC) shows that the probability of pembrolizumab + CT being cost-effective compared to CT at £20,000 WTP threshold was [redacted]% and increases to [redacted]% at the £30,000 WTP threshold (Figure 7).

Figure 6. Cost effectiveness plane, pembrolizumab + CT versus CT: pMMR (EAG base case)

Figure 7: Cost effectiveness acceptability curve, pembrolizumab + CT versus CT: pMMR (EAG base case)

EAG exploratory analyses pMMR subgroup

Table shows the results of the EAG's exploratory analyses for the pMMR subgroup.

Table 18: EAG Exploratory Analyses, pMMR

Parameter varied	Base case value	Scenario value	Rationale	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Percentage change in ICER
Company base case				[redacted]	1.21	[redacted]	
Treatment waning in OS	No treatment waning assumed	**Scenario 1** Gradual waning 5 to 7 years after starting treatment for all patients (**EAG base case**)	Precedent in previous NICE EC appraisals where patients discontinue treatment with immunotherapy after two years	[redacted]	0.62	[redacted]	[redacted]
		Scenario 2 Complete loss of treatment effect 5 years after starting treatment for all patients	EAG clinical expert 1	[redacted]	0.53	[redacted]	[redacted]
		Scenario 3 Gradual waning 3-5 years after starting	EAG clinical expert 2	[redacted]	0.41	[redacted]	[redacted]

Parameter varied	Base case value	Scenario value	Rationale	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Percentage change in ICER
		treatment for all patients					
		Scenario 4 Gradual waning 5 to 7 years after starting treatment for patients with non-CR	Scenario 1 applied to non-CR responders	[redacted]	0.70	[redacted]	[redacted]
		Scenario 5 Complete loss of treatment effect 5 years after starting treatment for patients with non-CR	EAG clinical expert 1 preference applied to non-CR patients	[redacted]	0.63	[redacted]	[redacted]
		Scenario 6 Gradual waning 3-5 years after starting treatment for non-CR patients	EAG clinical expert 2 preference applied to non-CR patients	[redacted]	0.53	[redacted]	[redacted]

All-comer

The EAG's adjustments to the company's base case model for the all-comer population are presented in Table 19, showing the individual effect of each change as well as the combined effect of all changes cumulatively for all-comer population. Table 20 and Table 21 show the EAG's estimated deterministic and probabilistic ICERs respectively.

The EAG's deterministic ICER for the all-comer population was [redacted]/QALY, representing a [redacted]% increase from the company's base case ICER. The most influential adjustment was the choice of OS extrapolation for Pembrolizumab+CT arm followed by treatment waning assumption. Retaining the utilities used in company's original submission, based on KN-158 trial had minimal impact on the base case ICER.

The probability of cost-effectiveness for pembrolizumab +CT at a WTP threshold of £20,000/QALY and £30,000/QALY was [redacted]% and [redacted]% respectively.

Table 19. EAG preferred model assumptions: All-comer population

Preferred assumption	ICER (£/QALY)	Section in EAG report	Impact on company base case
Company base case ICER	[redacted]		
EAG 01: OS extrapolation for pembrolizumab +CT using a piecewise approach (log-logistic model with 9.4 week cut)	[redacted]		[redacted]
Treatment waning from 5-7 years for all patients.	[redacted]	1.8	[redacted]
Utilities: KN-158 PFS: [redacted] PD: [redacted]	[redacted]	1.7	[redacted]
EAG base case (All changes applied)	[redacted]		[redacted]

Table 20. EAG deterministic base case cost-effectiveness analysis (with PAS price used for pembrolizumab), All-comer

Technologies	Total costs, £	Total LYG	Total QALYs	Inc costs, £	Inc LYG	Inc QALYs	ICER (£/QALY)
Pembrolizumab + CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.71	[redacted]
CT	[redacted]	3.79	[redacted]	-	-	-	-

Table 21. EAG Mean probabilistic cost-effectiveness estimates: all-comer

Treatment	Costs	Lys	QALYs	Incremental costs	Incremental Lys	Incremental QALYs	ICER
Pembrolizumab + Carboplatin + Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.68	[redacted]
Carboplatin + Paclitaxel	[redacted]	3.75	[redacted]	-	-	-	-

[redacted]

Figure 8. Cost-effectiveness acceptability curve, pembrolizumab+CT vs. CT: all-comer population EAG base case

Figure 9. Cost-effectiveness scatterplot, pembrolizumab+CT vs. CT: all-comer population EAG base case

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